DESCRIPTION

PREVENTIVE/REMEDY FOR CANCER

Technical Field

[0001]

The present invention relates to an agent for preventing or treating a trastuzumab-resistant cancer, which comprises one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a RHO inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor, and the like.

Background Art

[0002]

At present, trastuzumab (trade mark: herceptin), which is a conventional HER2 inhibitor, has been widely used for HER2-expressing cancer. However, it is known that certain cancers do not respond to trastuzumab even if it expresses HER2, and even HER2-dependent cancers, for which trastuzumab is effective, acquire resistance to trastuzumab during continuous treatment therewith (non-patent document 1). As the mechanism of acquiring resistance to HER2 inhibitor, overexpression of MUC4, compensatory signal transduction by other HER family, compensatory signal transduction by IGF-1 receptor, and altered downstream signaling pathway via PTEN/Akt are known (non-patent document 1, non-patent document 2). With these mechanisms, however, the aforementioned trastuzumab resistance cannot be explained.

[0003]

As HER2 inhibitors, patent documents 1-3 disclose condensed pyrimidine derivatives. In addition, patent document 4 discloses a concomitant drug using such condensed pyrimidine derivative. However, a HER2 inhibitor still effective against the aforementioned trastuzumab-resistant cancer has not been reported heretofore.

[0004]

Non-patent document 3 describes that EGF receptor signals are transmitted to Cofilin sequentially via Rho, ROCK, PAK and

LIMK. Non-patent document 4 reports that the Rho/ROCK system is involved in the metastasis of cancer cells. Non-patent documents 5-7 describe anticancer action of a small-molecule Rho inhibitor (CCG-1423), anticancer action of a small-molecule Rho/ROCK inhibitor (Y-27632) in a liver cancer model and anticancer action of a small-molecule ROCK inhibitor (Wf-536) (suppression of metastasis of melanoma to lung cancer), respectively.

However, the connection between the trastuzumab-resistant cancer and the signal transduction pathway has not been known heretofore.

patent document 1: WO 2005/118588

patent document 2: WO 2007/073879

patent document 3: US 12/005,883

patent document 4: WO 2008/044782

non-patent document 1: Breast Cancer Research, 2006, 8: 215

non-patent document 2: Nature Clinical Practice Oncology, 2006, 3: 269

non-patent document 3: Nature Review 7, p431, 2007

non-patent document 4: FEBS Letters 580, p4252, 2006

non-patent document 5: Mol Cancer Ther 6, p2249, 2007

non-patent document 6: Hepatology Research 2008

non-patent document 7: Cancer Chemother Pharmacol 52, p319, 2003

Disclosure of the Invention

Problems to be Solved by the Invention

[0005]

Administration of trastuzumab, which is a conventional HER2 inhibitor, to HER2 positive cancer cells causes resistance to the HER2 inhibitor in the cancer cells. The present invention aims to provide an agent for preventing or treating HER2 positive cancer, which is effective against such trastuzumab-resistant cancer.

Means of Solving the Problems

[0006]

The present inventors have conducted intensive studies and found that inhibition of cofilin or an enzyme (PAK1, LIMK, RHO, ROCK1, ROCK2) present at the upstream of cofilin in the cytoskeletal signaling is useful for the prophylaxis or treatment of trastuzumab-resistant cancer, and that a HER2 inhibitor including compound N-{2-[4-({3-chloro-4-[3-(trifluoromethyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide (compound A) alone is useful for the prophylaxis or treatment of trastuzumab-resistant cancer. They have further studied and completed the present invention.

[0007]

Accordingly, the present invention relates to in the following.

[1] An agent for preventing or treating a trastuzumab-resistant cancer, comprising one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a RHO inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor.

[2] The agent of the above-mentioned [1], comprising a cofilin inhibitor.

[3] The agent of the above-mentioned [1], comprising a PAK1 inhibitor.

[4] The agent of the above-mentioned [1], comprising a LIMK inhibitor.

[5] The agent of the above-mentioned [1], comprising a RHO inhibitor.

[6] The agent of the above-mentioned [1], comprising a ROCK1 inhibitor.

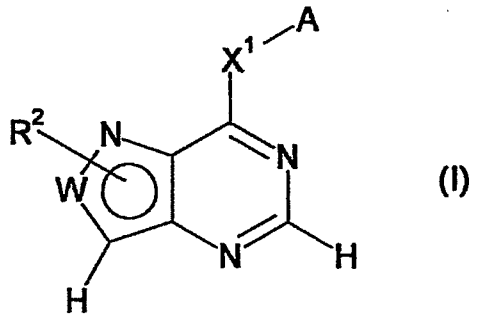
[7] The agent of the above-mentioned [1], comprising a ROCK2 inhibitor.

[8] A combination drug comprising (1) a HER2 inhibitor and (2) one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a RHO inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor.

[9] The drug of the above-mentioned [8], wherein the HER2 inhibitor is trastuzumab or lapatinib.

[10] The drug of the above-mentioned [8], wherein the HER2 inhibitor is a compound represented by the formula

[0008]



(I)

[0009]

wherein W is $C(R^1)$ or N,

A is an optionally substituted aryl group or an optionally substituted heteroaryl group,

X^1 is $-NR^3-Y^1-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-CHR^3-$

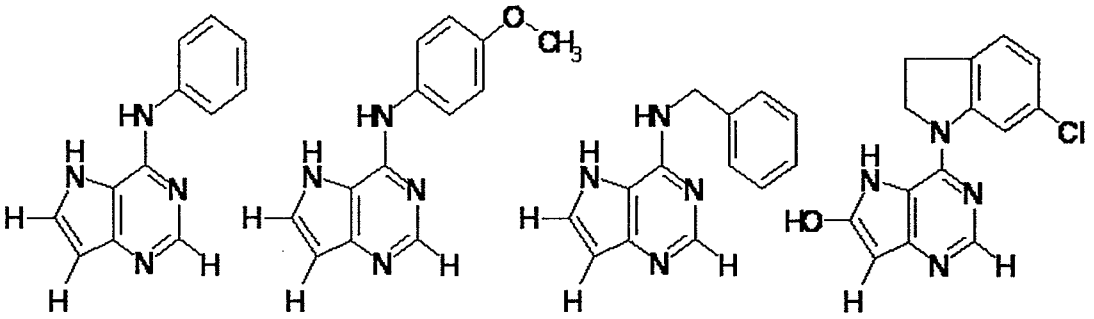
wherein R^3 is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or R^3 is optionally bonded to a carbon atom or hetero atom on an aryl group or heteroaryl group for A to form an optionally substituted ring structure,

Y^1 is a single bond or C_{1-4} alkylene or $-O-(C_{1-4}$ alkylene$)-$, each of which is optionally substituted,

R^1 is a hydrogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom, and R^2 is a hydrogen atom, or an optionally substituted group bonded via a carbon atom or a sulfur atom, or

R^1 and R^2, or R^2 and R^3 are optionally bonded to each other to form an optionally substituted ring structure, except a compound represented by the formula

[0010]

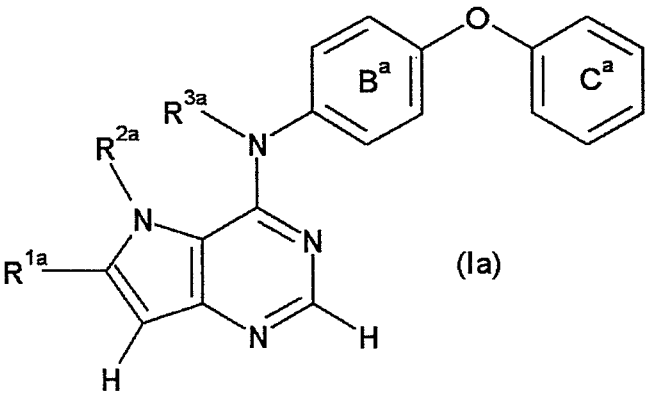


[0011]

or a salt thereof.

[11] The drug of the above-mentioned [8], wherein the HER2 inhibitor is a compound represented by the formula

[0012]



(Ia)

[0013]

wherein

R^{1a} is a hydrogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

R^{2a} is an optionally substituted group bonded via a carbon atom or a sulfur atom, or

R^{1a} and R^{2a}, or R^{2a} and R^{3a} are optionally bonded to each other to form an optionally substituted ring structure,

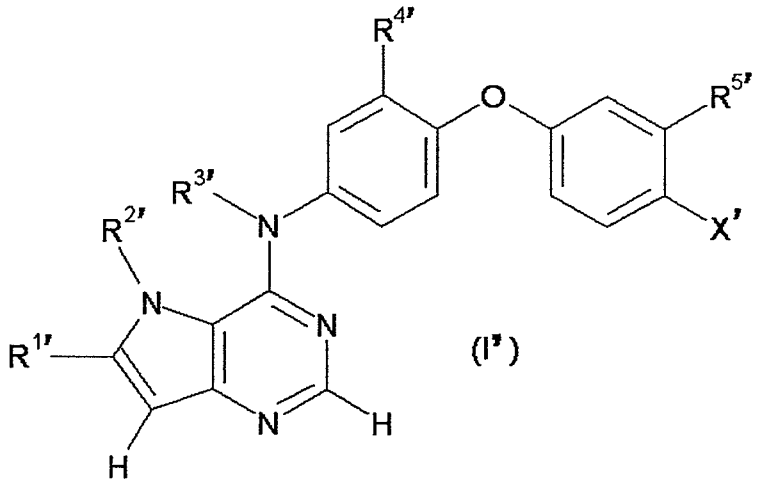
R^{3a} is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or R^{3a} is optionally bonded via a carbon atom of the adjacent phenyl group to form an optionally substituted ring structure,

B^a is an optionally substituted benzene ring, and C^a is an optionally substituted C_{6-18} aryl group, or a salt thereof.

[12] The drug of the above-mentioned [8], wherein the HER2

inhibitor is a compound represented by the formula

[0014]



(I')

[0015]

wherein

$R^{1'}$ is a hydrogen atom,

$R^{2'}$ is a C_{1-6} alkyl group substituted by a group represented by $-NR^{6'}-CO-(CH_2)_n-SO_2-$(optionally halogenated C_{1-4} alkyl) wherein n is an integer of 1 to 4, $R^{6'}$ is a hydrogen atom or a C_{1-4} alkyl group, wherein $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

$R^{3'}$ is a hydrogen atom or a C_{1-6} alkyl group,

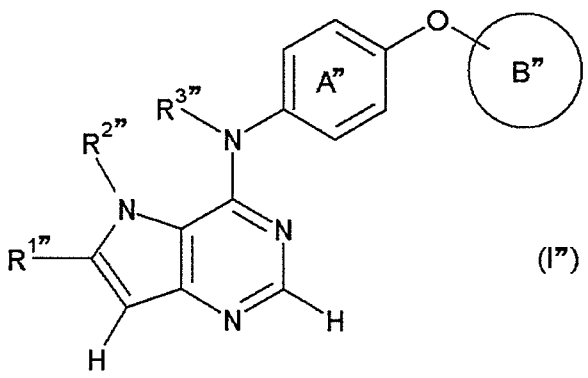
$R^{4'}$ is a halogen atom or a C_{1-6} alkyl group,

$R^{5'}$ is a halogen atom or a C_{1-6} alkyl group, and

X' is a hydrogen atom or a halogen atom, except N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide, or a salt thereof.

[13] The drug of the above-mentioned [8], wherein the HER2 inhibitor is a compound represented by the formula

[0016]



(I")

[0017]

wherein

$R^{1"}$ is a hydrogen atom, a halogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

$R^{2"}$ is a hydrogen atom, or an optionally substituted group bonded via a carbon atom or a sulfur atom,

or $R^{1"}$ and $R^{2"}$, or $R^{2"}$ and $R^{3"}$ are optionally bonded to each other to form an optionally substituted ring structure;

$R^{3"}$ is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or

$R^{3"}$ is optionally bonded to a carbon atom of ring A" to form an optionally substituted ring structure;

ring A" is an optionally substituted benzene ring;

ring B" is (i) an optionally substituted fused ring, or

(ii) a pyridine ring having optionally substituted carbamoyl wherein the pyridine ring is optionally further substituted, or a salt thereof.

[14] The drug of the above-mentioned [8], wherein the HER2 inhibitor is N-{2-[4-({3-chloro-4-[3-(trifluoromethyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide or a salt thereof.

[15] The drug of the above-mentioned [8], which is an agent for preventing or treating HER2-expressing cancer.

[16] A method of preventing or treating trastuzumab-resistant

cancer, which comprises inhibiting one or more selected from cofilin, PAK1, LIMK, RHO, ROCK1 and ROCK2.

[17] The method of the above-mentioned [16], which comprises administering an effective amount of one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a RHO inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor to a mammal.

[18] Use of one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a RHO inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor for the production of an agent for preventing or treating a trastuzumab-resistant cancer.

[19] A method of examining the sensitivity of a HER2-expressing cancer to a HER2 inhibitor, comprising measuring the expression or activation state of one or more selected from cofilin, PAK1, LIMK, RHO, ROCK1 and ROCK2 in a sample collected from an animal having the cancer.

[20] A method of treating a cancer in an animal judged to be low sensitive to a HER2 inhibitor by the method of the above-mentioned [19], which comprises administering an effective amount of each of (1) a HER2 inhibitor, and (2) one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a RHO inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor to the animal.

[21] A method of screening for a drug for the prophylaxis or treatment of a trastuzumab-resistant cancer, comprising measuring and comparing the expression, activation state or activity of one or more selected from cofilin, PAK1, LIMK, RHO, ROCK1 and ROCK2 in a cell in the presence or absence of a test compound.

[22] An agent for preventing or treating a trastuzumab-resistant cancer, comprising N-{2-[4-({3-chloro-4-[3-(trifluoromethyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide or a salt thereof.

[23] A method of treating a trastuzumab-resistance cancer in a mammal, comprising administering an effective amount of N-{2-[4-({3-chloro-4-[3-(trifluoromethyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide or a salt thereof to the animal.

Effect of the Invention

[0018]

An agent for preventing or treating a trastuzumab-resistant cancer of the present invention, which comprises one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor, can be used effectively for the prophylaxis or treatment of a trastuzumab-resistant cancer not only by a single use but also in combination with a conventional HER2 inhibitor. In addition, even compound A alone can be used for the prophylaxis or treatment of a trastuzumab-resistant cancer.

Brief Description of the Drawings

[0019]

Fig. 1 shows that the sensitivity to a HER2 inhibitor is enhanced and a HER2 inhibitor becomes effective against low sensitive cell line by knockdown of LIMK1 with LIMK1 siRNA, wherein -●-: high sensitive cell line, LIMK1 siRNA; -■-: low sensitive cell line, LIMK1 siRNA; -O-: high sensitive cell line, control siRNA; -□-: low sensitive cell line, control siRNA.

Fig. 2 shows that the sensitivity to a HER2 inhibitor is enhanced by knockdown of PAK1 with PAK1 siRNA, wherein -●-: high sensitive cell line, PAK1 siRNA; -■-: low sensitive cell line, PAK1 siRNA; -O-: high sensitive cell line, control siRNA; -□-: low sensitive cell line, control siRNA.

Fig. 3 shows that the sensitivity to a HER2 inhibitor is enhanced by knockdown of cofilin1 with cofilin1 siRNA, wherein -●-: high sensitive cell line, cofilin1 siRNA; -■-: low sensitive cell line, cofilin1 siRNA; -O-: high sensitive cell

line, control siRNA; -□-: low sensitive cell line, control siRNA.

Fig. 4 shows that the sensitivity to a HER2 inhibitor is enhanced and a HER2 inhibitor becomes effective against low sensitive cell line by knockdown of Rho with Rho siRNA.

Fig. 5 shows that the sensitivity to a HER2 inhibitor is enhanced by knockdown of ROCK1 with ROCK1 siRNA.

Fig. 6 shows that the sensitivity to a HER2 inhibitor is enhanced by knockdown of ROCK2 with ROCK2 siRNA.

In Fig. 7, the left figure shows that high sensitive cell line and low sensitive cell line are different in the sensitivity against trastuzumab, and the right figure shows that the proliferation of both the high sensitive cell line and the low sensitive cell line is suppressed in a concentration-dependent manner by the addition of compound A.

In Fig. 8, the left figure shows that high sensitive cell line and low sensitive cell line are different in the sensitivity against trastuzumab, and the right figure shows that the proliferation of both the high sensitive cell line and the low sensitive cell line is suppressed in a concentration-dependent manner by the addition of lapatinib.

[0020]

(Detailed Description of the Invention)

Cofilin in the present invention includes two isoforms of a protein comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by SEQ ID NO:2 (cofilin 1; also referred to as CFL1) and a protein comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by SEQ ID NO:4 (cofilin 2; also referred to as CFL2).

PAK1 (p21-activated kinase 1) in the present invention is a protein comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by SEQ ID NO: 6.

LIMK (LIM domain kinase) in the present invention includes two isoforms of a protein (LIMK1) comprising the same

or substantially the same amino acid sequence as the amino acid sequence shown by the amino acid sequence shown by SEQ ID NO: 8 and a protein (LIMK2) comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by SEQ ID NO: 10.

RHO (Ras homolog) in the present invention is a protein (RHO) comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by SEQ ID NO: 12.

ROCK (Rho-associated, coiled-coil containing protein kinase) in the present invention includes two isoforms of a protein (ROCK1) comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by the amino acid sequence shown by SEQ ID NO: 14 and a protein (ROCK2) comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by SEQ ID NO: 16.

Herein, proteins and peptides are described with the left end indicating the N-terminus (amino terminus) and the right end indicating the C-terminus (carboxyl terminus), according to the common practice of peptide designation.

[0021]

The "amino acid sequence substantially the same as the amino acid sequence shown by SEQ ID NO: 2" means a natural allele variant or polymorphism of human CFL1 (RefSeq Accession No. NP_005498.1) consisting of the amino acid sequence shown by SEQ ID NO: 2 (same for chimpanzee and dogs), its ortholog in other warm-blooded animal [for example, mouse ortholog (having 98.8% identity with human CFL1 at amino acid level) registered with GenBank under RefSeq Accession No. NP_031713.1, rat ortholog (having 99.4% identity with human CFL1 at amino acid level) registered under RefSeq Accession No. NP_058843.1 and the like], and a natural allele variant or polymorphism of the ortholog.

The "amino acid sequence substantially the same as the amino acid sequence shown by SEQ ID NO: 4" means a natural

allele variant or polymorphism of human CFL2 (RefSeq Accession No. NP_068733.1) consisting of the amino acid sequence shown by SEQ ID NO: 4 (same for dogs), its ortholog in other warm-blooded animal [for example, mouse ortholog (having 99.4% identity with human CFL2 at amino acid level) registered with GenBank under RefSeq Accession No. NP_031714.1, rat ortholog (having 99.4% identity with human CFL2 at amino acid level) registered under RefSeq Accession No. XP_345675.3, chimpanzee ortholog (having 100% identity with human CFL2 in the overlapped region at amino acid level) registered under RefSeq Accession No. XP_509898.1, chicken ortholog (having 97.0% identity with human CFL2 at amino acid level) registered under RefSeq Accession No. NP_001004406.1 and the like], and a natural allele variant or polymorphism of the ortholog.

The "amino acid sequence substantially the same as the amino acid sequence shown by SEQ ID NO: 6" means a natural allele variant or polymorphism of human PAK1 (RefSeq Accession No. NP_002567.3) consisting of the amino acid sequence shown by SEQ ID NO: 6, its ortholog in other warm-blooded animal [for example, mouse ortholog (having 97.6% identity with human PAK1 at amino acid level) registered with GenBank under RefSeq Accession No. NP_035165.1, rat ortholog (having 98.9% identity with human PAK1 at amino acid level) registered under RefSeq Accession No. NP_058894.1, dog ortholog (having 96.7% identity with human PAK1 at amino acid level) registered under RefSeq Accession No. XP_849651.1, chimpanzee ortholog (having 93.9% identity with human PAK1 at amino acid level) registered under RefSeq Accession No. XP_508657.2, chicken ortholog (having 94.3% identity with human PAK1 at amino acid level) registered under RefSeq Accession No. XP_417275.1 and the like], and a natural allele variant or polymorphism of the ortholog.

The "amino acid sequence substantially the same as the amino acid sequence shown by SEQ ID NO: 8" means a natural allele variant or polymorphism of human LIMK1 (RefSeq Accession No. NP_002305.1) consisting of the amino acid

sequence shown by SEQ ID NO: 8, its ortholog in other warm-blooded animal [for example, mouse ortholog (having 95.2% identity with human LIMK1 at amino acid level) registered with GenBank under RefSeq Accession No. NP_034847.1, rat ortholog (having 95.2% identity with human LIMK1 at amino acid level) registered under RefSeq Accession No. NP_113915.1, dog ortholog (having 94.1% identity with human LIMK1 at amino acid level) registered under RefSeq Accession No. XP_849646.1, chimpanzee ortholog (having 98.6% identity with human LIMK1 at amino acid level) registered under RefSeq Accession No. XP_00114876.1 and the like], and a natural allele variant or polymorphism of the ortholog.

The "amino acid sequence substantially the same as the amino acid sequence shown by SEQ ID NO: 10" means a natural allele variant or polymorphism of human LIMK2 (RefSeq Accession No. NP_005560.1) consisting of the amino acid sequence shown by SEQ ID NO: 10, its ortholog in other warm-blooded animal [for example, mouse ortholog (having 93.1% identity with human LIMK2 at amino acid level) registered with GenBank under RefSeq Accession No. NP_034848.1, rat ortholog (having 92.9% identity with human LIMK2 at amino acid level) registered under RefSeq Accession No. NP_077049.2, dog ortholog (having 95.5% identity with human LIMK2 at amino acid level) registered under RefSeq Accession No. XP_852696.1 and the like], and a natural allele variant or polymorphism of the ortholog.

The "amino acid sequence substantially the same as the amino acid sequence shown by SEQ ID NO: 12" means a natural allele variant or polymorphism of human Rho (RefSeq Accession No. NP_001655.1) consisting of the amino acid sequence shown by SEQ ID NO: 12, its ortholog in other warm-blooded animal [for example, mouse ortholog (having 99.5% identity with human Rho at amino acid level) registered with GenBank under RefSeq Accession No. NP_058082.2, rat ortholog (having 99.5% identity with human Rho at amino acid level) registered under RefSeq

Accession No. NP_476473.1, dog ortholog (having 99.5% identity with human Rho at amino acid level) registered under RefSeq Accession No. NP_001003273.1 and the like], and a natural allele variant or polymorphism of the ortholog.

The "amino acid sequence substantially the same as the amino acid sequence shown by SEQ ID NO: 14" means a natural allele variant or polymorphism of human ROCK1 (RefSeq Accession No. NP_005397.1) consisting of the amino acid sequence shown by SEQ ID NO: 14, its ortholog in other warm-blooded animal [for example, mouse ortholog (having 96.6% identity with human ROCK1 at amino acid level) registered with GenBank under RefSeq Accession No. NP_033097.1, rat ortholog (having 94.8% identity with human ROCK1 at amino acid level) registered under RefSeq Accession No. NP_112360.1, chimpanzee ortholog (having 99.9% identity with human ROCK1 at amino acid level) registered under RefSeq Accession No. XP_512051.2 and the like], and a natural allele variant or polymorphism of the ortholog.

The "amino acid sequence substantially the same as the amino acid sequence shown by SEQ ID NO: 16" means a natural allele variant or polymorphism of human ROCK2 (RefSeq Accession No. NP_004841.2) consisting of the amino acid sequence shown by SEQ ID NO: 16, its ortholog in other warm-blooded animal [for example, mouse ortholog (having 96.8% identity with human ROCK2 at amino acid level) registered with GenBank under RefSeq Accession No. NP_033098.2, bovine ortholog (having 97.8% identity with human ROCK2 at amino acid level) registered under RefSeq Accession No. NP_776877.1, chimpanzee ortholog (having 99.9% identity with human Rho at amino acid level) registered under RefSeq Accession No. XP_525689.2, rat ortholog (having 96.4% identity with human Rho at amino acid level) registered under RefSeq Accession No. NP_037154.1 and the like], and a natural allele variant or polymorphism of the ortholog.

[0022]

In the present specification, cofilin (CFL1 and CFL2), PAK1, LIMK (LIMK1 and LIMK2), and Rho and ROCK (ROCK1 and ROCK2) are comprehensively sometimes to be abbreviated as "the target protein of the present invention", and the gene encoding same is abbreviated as the "target gene of the present invention".

[0023]

In the present specification, the cofilin inhibitor refers to a substance that inhibits expression, activation (phosphorylation) or action of cofilin in cytoskeletal signaling. Here, the "inhibition of activation" includes dephosphorylation.

In the present specification, the PAK1 inhibitor refers to a substance that inhibits expression, activation (phosphorylation) or action of PAK1 in cytoskeletal signaling. Here, the "inhibition of activation" includes dephosphorylation.

In the present specification, the LIMK inhibitor refers to a substance that inhibits expression, activation (phosphorylation) or action of LIMK in cytoskeletal signaling. Here, the "inhibition of activation" includes dephosphorylation.

In the present specification, the Rho inhibitor refers to a substance that inhibits expression, activation (phosphorylation) or action of Rho in cytoskeletal signaling. Here, the "inhibition of activation" includes dephosphorylation.

In the present specification, the ROCK (ROCK1 and ROCK2) inhibitor refers to a substance that inhibits expression, activation (phosphorylation) or action of ROCK in cytoskeletal signaling. Here, the "inhibition of activation" includes dephosphorylation.

[0024]

In the present invention, "a substance that inhibits the expression of target protein of the present invention" may be

one that acts in any stage at the target gene transcription level, post-transcriptional regulation level, translation-into-protein level, post-translational modification level and the like. Therefore, examples of a substance that inhibits the expression of target protein include a substance that inhibits the transcription of the target gene, a substance that inhibits the processing of the primary transcription product into mRNA, a substance that inhibits the transportation of mRNA to cytoplasm, a substance that promotes the degradation of mRNA, a substance that inhibits the translation of mRNA into protein, a substance that inhibits the post-translational modification of target polypeptide and the like. Although any one that acts in any stage can be preferably used, a substance that inhibits the translation of mRNA into protein is preferred in that the production of target protein is directly inhibited.

[0025]

As a substance capable of specifically inhibiting the translation of the mRNA of target gene into protein, preferably, a nucleic acid comprising a base sequence complementary or substantially complementary to the base sequence of one of these mRNAs or a portion thereof can be mentioned.

As a base sequence of CFL1 gene mRNA, the same or substantially the same base sequence as the base sequence shown by SEQ ID NO: 1 (human CFL1) can be mentioned. Here, the "substantially the same base sequence" refers to the base sequence of an ortholog, natural allele variant or polymorphism in other warm-blooded animal, as in the aforementioned target protein of the present invention.

As a base sequence of CFL2 gene mRNA, the same or substantially the same base sequence as the base sequence shown by SEQ ID NO: 3 (human CFL2) can be mentioned. Here, the "substantially the same base sequence" refers to the base sequence of an ortholog, natural allele variant or

polymorphism in other warm-blooded animal, as in the aforementioned target protein of the present invention.

As a base sequence of PAK1 gene mRNA, the same or substantially the same base sequence as the base sequence shown by SEQ ID NO: 5 (human PAK1) can be mentioned. Here, the "substantially the same base sequence" refers to the base sequence of an ortholog, natural allele variant or polymorphism in other warm-blooded animal, as in the aforementioned target protein of the present invention.

As a base sequence of LIMK1 gene mRNA, the same or substantially the same base sequence as the base sequence shown by SEQ ID NO: 7 (human LIMK1) can be mentioned. Here, the "substantially the same base sequence" refers to the base sequence of an ortholog, natural allele variant or polymorphism in other warm-blooded animal, as in the aforementioned target protein of the present invention.

As a base sequence of LIMK2 gene mRNA, the same or substantially the same base sequence as the base sequence shown by SEQ ID NO: 9 (human LIMK2) can be mentioned. Here, the "substantially the same base sequence" refers to the base sequence of an ortholog, natural allele variant or polymorphism in other warm-blooded animal, as in the aforementioned target protein of the present invention.

As a base sequence of Rho gene mRNA, the same or substantially the same base sequence as the base sequence shown by SEQ ID NO: 11 (human Rho) can be mentioned. Here, the "substantially the same base sequence" refers to the base sequence of an ortholog, natural allele variant or polymorphism in other warm-blooded animal, as in the aforementioned target protein of the present invention.

As a base sequence of ROCK1 gene mRNA, the same or substantially the same base sequence as the base sequence shown by SEQ ID NO: 13 (human ROCK1) can be mentioned. Here, the "substantially the same base sequence" refers to the base sequence of an ortholog, natural allele variant or

polymorphism in other warm-blooded animal, as in the aforementioned target protein of the present invention.

As a base sequence of the ROCK2 gene mRNA, the same or substantially the same base sequence as the base sequence shown by SEQ ID NO: 15 (human ROCK2) can be mentioned. Here, the "substantially the same base sequence" refers to the base sequence of an ortholog, natural allele variant or polymorphism in other warm-blooded animal, as in the aforementioned target protein of the present invention.

A base sequence substantially complementary to the base sequence of the mRNA of the target gene means a base sequence having a complementarity such that the base sequence is capable of binding to the target sequence for the mRNA to inhibit the translation thereof; specifically, for example, the base sequence is a base sequence having a homology of about 80% or more, preferably about 90% or more, more preferably about 95% or more, and most preferably about 98% or more, with respect to the overlapping region, to a base sequence completely complementary to the base sequence of the mRNA (i.e., the base sequence of a complementary strand of the mRNA).

Homology of the base sequences in the present specification can be calculated under the following conditions (an expectation value = 10; gaps are allowed; filtering = ON; match score = 1; mismatch score = -3) using a homology calculating algorithm NCBI BLAST (National Center for Biotechnology Information Basic Local Alignment Search Tool). As examples of other algorithms for determination of base sequence homology, the algorithm described in Karlin et al., Proc. Natl. Acad. Sci. USA, 90:5873-5877 (1993) [the algorithm is incorporated in the NBLAST and XBLAST programs (version 2.0) (Altschul et al., Nucleic Acids Res., 25:3389-3402 (1997))], the algorithm described in Needleman et al., J. Mol. Biol., 48:444-453 (1970) [the algorithm is incorporated in the GAP program in the GCG software package], the algorithm

described in Myers and Miller, CABIOS, 4:11-17 (1988) [the algorithm is incorporated in the ALIGN program (version 2.0), which is part of the CGC sequence alignment software package], and the algorithm described in Pearson et al., Proc. Natl. Acad. Sci. USA, 85:2444-2448 (1988) [the algorithm is incorporated in the FASTA program in the GCG software package] and the like can be mentioned, and these can also be preferably used in the same way.

[0026]

More specifically, as a base sequence complementary or substantially complementary to the base sequence of the mRNA of the target gene, a base sequence complementary or substantially complementary to (a) the base sequence encoding the target gene or (b) a base sequence that hybridizes with the complementary chain of the base sequence under highly stringent conditions and encodes a protein having substantially the same quality of activity as the target protein can be mentioned. Here, "substantially the same quality of activity" is as defined above.

Highly stringent conditions refer to, for example, conditions involving a sodium concentration of about 19 to about 40mM, preferably about 19 to about 20mM, and a temperature of about 50 to about 70°C, preferably about 60 to about 65°C. In particular, a preferred case is such that the sodium salt concentration is about 19mM and the temperature is about 65°C.

[0027]

"A portion of a base sequence complementary or substantially complementary to the base sequence of the mRNA of the target gene" is not particularly limited with respect to the length and position thereof, as far as the portion is capable of binding specifically to the mRNA of the target gene, and capable of inhibiting the protein translation from the mRNA; in terms of sequence specificity, the portion comprises at least 10 bases or more, preferably about 15 bases or more,

and more preferably about 20 bases or more, of a portion complementary or substantially complementary to the target sequence.

[0028]

Specifically, as a nucleic acid comprising a base sequence complementary or substantially complementary to the base sequence of the mRNA of the target gene or a portion thereof, any one of the following (a) to (c) can be preferably mentioned.

(a) An antisense nucleic acid against the mRNA of the target gene

(b) An siRNA against the mRNA of the target gene

(c) A nucleic acid capable of producing an siRNA against the mRNA of the target gene

[0029]

(a) An antisense nucleic acid against the mRNA of the target gene

"An antisense nucleic acid against the mRNA of the target gene" in the present invention is a nucleic acid comprising a base sequence complementary or substantially complementary to the base sequence of the mRNA or a portion thereof, and having the function of suppressing protein synthesis by binding to the target mRNA while forming a specific and stable double strand therewith.

Examples of the antisense nucleic acid include polydeoxyribonucleotides comprising 2-deoxy-D-ribose, polyribonucleotides comprising D-ribose, other types of polynucleotides being N-glycosides of the purine or pyrimidine base, other polymers having a non-nucleotide backbone (for example, commercially available protein nucleic acids and nucleic acid polymers specific for synthetic sequences) or other polymers comprising a special linkage (provided that the polymers comprise nucleotides having such an alignment that allows base pairing or base attachment, as found in DNA or RNA) and the like. These may be double-stranded DNAs, single-

stranded DNAs, double-stranded RNAs, single-stranded RNAs, or DNA:RNA hybrids, and may also be unmodified polynucleotides (or unmodified oligonucleotides); those with known modifications, for example, those with labels known in the art, those with caps, those methylated, those with substitution of one or more naturally occurring nucleotides with their analogues, those with intramolecular modifications of nucleotides such as those with uncharged linkages (for example, methyl phosphonates, phosphotriesters, phosphoramidates, carbamates and the like) and those with charged linkages or sulfur-containing linkages (e.g., phosphorothioates, phosphorodithioates and the like); those having side chain groups such as proteins (e.g., nucleases, nuclease inhibitors, toxins, antibodies, signal peptides, poly-L-lysine and the like) or saccharides (e.g., monosaccharides and the like); those with intercalators (e.g., acridine, psoralen and the like); those with chelators (for example, metals, radioactive metals, boron, oxidative metals and the like); those with alkylating agents; or those with modified linkages (for example, α anomeric nucleic acids and the like). Here, "nucleosides", "nucleotides" and "nucleic acids" may include those not only comprising the purine and pyrimidine bases, but also comprising other modified heterocyclic bases. Such modified products may comprise a methylated purine and pyrimidine, an acylated purine and pyrimidine, and other heterocyclic ring. Modified nucleosides and modified nucleotides may have a modification in the sugar moiety thereof; for example, one or more hydroxyl groups may be substituted by halogens, aliphatic groups and the like, or may be converted into functional groups such as ethers and amines.

[0030]

As stated above, the antisense nucleic acid may be a DNA or RNA, or a DNA/RNA chimera. When the antisense nucleic acid is a DNA, a RNA:DNA hybrid formed by a target RNA and antisense DNA can be recognized by endogenous RNase H to cause

selective degradation of the target RNA. Therefore, in the case of an antisense DNA intended to cause degradation by RNase H, the target sequence may be not only a sequence in the mRNA, but also the sequence of an intron region in the primary translation product of the target gene.

[0031]

The target region for an antisense nucleic acid of the present invention is not particularly limited with respect to the length thereof, as far as the translation into target protein is inhibited as a result of hybridization of the antisense nucleic acid; the target region may be the entire sequence or a partial sequence of the mRNA that encodes the protein, and the length is about 10 bases for the shortest, and the entire sequence of the mRNA or primary transcription product for the longest. Taking into account the issues of the ease of synthesis, antigenicity, and internalization and the like, an oligonucleotide consisting of about 10 to about 40 bases, particularly about 15 to about 30 bases, is preferable, but this is not to be construed as limiting. Specifically, the 5′ end hairpin loops, 5′ end 6-base-pair repeats, 5′ untranslated regions, translation initiation codons, protein coding regions, ORF translation stop codons, 3′ untranslated regions, 3′ end palindrome regions, 3′ end hairpin loops and the like of the target gene can be chosen as preferable target regions for the antisense nucleic acid, but these are not to be construed as limiting.

[0032]

Furthermore, an antisense nucleic acid of the present invention may be one that not only hybridizes with the mRNA or primary transcription product of the target gene to inhibit the translation into protein, but also is capable of binding to these genes, which are double-stranded DNAs, to form a triple strand (triplex) and inhibit the transcription into RNA (anti-gene).

[0033]

Although the nucleotide molecules that constitute the antisense nucleic acid may be natural-type RNAs or DNAs, the molecules can comprise various chemical modifications in order to increase the stability (chemical and/or to-enzyme) or specific activity (affinity for RNA). For example, to prevent degradation by hydrolases such as nuclease, the phosphoric acid residue (phosphate) of each nucleotide that constitutes the antisense nucleic acid can be substituted with, for example, a chemically modified phosphoric acid residue such as phosphorothioate (PS), methylphosphonate, or phosphorodithionate. The hydroxyl group at the 2'-position of the sugar (ribose) of each nucleotide may be replaced with -OR (R represents, for example, CH_3(2'-O-Me), $CH_2CH_2OCH_3$(2'-O-MOE), $CH_2CH_2NHC(NH)NH_2$, $CH_2CONHCH_3$, CH_2CH_2CN or the like). Furthermore, a base moiety (pyrimidine, purine) may be chemically modified; for example, introduction of a methyl group or a cationic functional group into the 5-position of the pyrimidine base, substitution of the 2-position carbonyl group with thiocarbonyl and the like can be mentioned.

[0034]

Regarding the conformation of the sugar moiety of RNA, two types are dominant: C2'-endo (S-type) and C3'-endo (N-type); in single-stranded RNA, the sugar moiety occurs in an equilibrium of the two types, but when a double strand is formed, the conformation is fixed for the type N. Therefore, BNA (LNA) (Imanishi, T. et al., Chem. Commun., 1653-9, 2002; Jepsen, J.S. et al., Oligonucleotides, 14, 130-46, 2004), or ENA (Morita, K. et al., Nucleosides Nucleotides Nucleic Acids, 22, 1619-21, 2003), an RNA derivative wherein the conformation of the sugar moiety is fixed to the type N by bridging the 2' oxygen and 4' carbon so as to confer strong bindability to the target RNA, can also be preferably used.

[0035]

An antisense oligonucleotide of the present invention can be prepared by determining the target sequence for the mRNA or

primary transcription product on the basis of the cDNA sequence or genomic DNA sequence of the target gene, and synthesizing a sequence complementary thereto using a commercially available automated DNA/RNA synthesizer (Applied Biosystems, Beckman and the like). All antisense nucleic acids comprising the aforementioned various modifications can be chemically synthesized by techniques known per se.

[0036]

(b) siRNA against mRNA of target gene

Herein, a double-stranded RNA consisting of an oligo-RNA complementary to the mRNA of the target gene and a complementary chain thereof, what is called an siRNA, is also defined as being included in nucleic acids comprising a base sequence complementary or substantially complementary to the base sequence of the mRNA of the target gene or a portion thereof. It had been known that so-called RNA interference (RNAi), which is a phenomenon wherein if short double-stranded RNA is introduced into a cell, mRNAs complementary to the RNA are degraded, occurs in nematodes, insects, plants and the like; since this phenomenon was confirmed to also occur widely in animal cells [Nature, 411(6836): 494-498 (2001)], RNAi has been widely utilized as an alternative technique to ribozymes. An siRNA can be designed as appropriate on the basis of base sequence information on the target mRNA using commercially available software (e.g., RNAi Designer; Invitrogen). Specifically, examples of preferable siRNAs of the present invention include, but are not limited to, siRNAs used in Examples described below and the like.

[0037]

Ribonucleoside molecules constituting an siRNA may also undergo the same modifications as in the above-described antisense nucleic acids in order to increase the stability, specific activity and the like. However, in the case of an siRNA, if all ribonucleoside molecules in the natural type RNA are substituted by the modified form, the RNAi activity is

sometimes lost, so that it is necessary that the minimum number of modified nucleosides be introduced to allow the RISC complex to function.

[0038]

An siRNA can be prepared by synthesizing a sense strand and antisense strand of a target sequence on the mRNA using an automated DNA/RNA synthesizer, respectively, and denaturing the strands in an appropriate annealing buffer solution at about 90 to about 95°C for about 1 minute, and thereafter annealing the strands at about 30 to about 70°C for about 1 to about 8 hours. An siRNA can also be prepared by synthesizing a short hairpin RNA (shRNA) serving as an siRNA precursor, and cleaving this using a dicer.

[0039]

(c) Nucleic acids capable of producing siRNA against mRNA of target gene

Herein, a nucleic acid designed to be capable of producing the above-described siRNA against the mRNA of the target gene in vivo is also defined as being included in nucleic acids comprising a base sequence complementary or substantially complementary to the base sequence of the mRNA of the target gene or a portion thereof. As such nucleic acids, the aforementioned shRNA, expression vectors constructed to express the shRNA and the like can be mentioned. An shRNA can be prepared by designing an oligo-RNA comprising a base sequence prepared by joining a sense chain and antisense chain of a target sequence on mRNA via a spacer sequence having a length allowing it to form an appropriate loop structure (for example, about 15 to 25 bases) inserted therebetween, and synthesizing this using an automated DNA/RNA synthesizer. An expression vector comprising an shRNA expression cassette can be prepared by preparing a double-stranded DNA that encodes the above-described shRNA by a conventional method, and thereafter inserting the DNA into an appropriate expression vector. As the shRNA expression vector, one having a Pol III

promoter such as U6 or H1 can be used. In this case, an shRNA transcribed in an animal cell carrying the expression vector forms a loop by itself, and is thereafter processed by an endogenous enzyme dicer and the like, whereby a mature siRNA is formed.

[0040]

As another preferred example of a nucleic acid comprising a base sequence complementary or substantially complementary to the base sequence of the mRNA of target gene or a portion thereof, a ribozyme capable of specifically cleaving the mRNA in the coding region can be mentioned. Although "ribozyme", in the narrow sense, refers to an RNA possessing enzymatic activity to cleave nucleic acids, the term is used herein as a concept encompassing any DNA possessing sequence-specific nucleic acid cleavage activity. The most versatile ribozyme is self-splicing RNA, which is found in infectious RNAs such as viroid and virusoid, and is known in the hammerhead type, hairpin type and the like. The hammerhead type exhibits enzyme activity with about 40 bases, and it is possible to specifically cleave only a target mRNA by rendering several bases at both ends adjacent to the hammerhead structure portion (about 10 bases in total) complementary to the desired cleavage site of mRNA. Because this type of ribozyme has RNA as the only substrate, the same has a further advantage that genomic DNA is never attacked. When the mRNA encoding the target protein of the present invention has a double strand structure by itself, the target sequence can be made to be single stranded by using a hybrid ribozyme coupled to an RNA motif derived from a virus nucleic acid capable of binding specifically to RNA helicase [Proc. Natl. Acad. Sci. USA, 98(10): 5572-5577 (2001)]. Furthermore, when ribozyme is used in the form of an expression vector comprising the DNA that encodes the same, the ribozyme may be a hybrid ribozyme further coupled with a sequence of altered tRNA to promote the localization of the transcription product to cytoplasm

[Nucleic Acids Res., 29(13): 2780-2788 (2001)].

[0041]

A nucleic acid comprising a base sequence complementary or substantially complementary to the base sequence of the mRNA of the target gene or a portion thereof can be supplied in a special form such as liposomes or microspheres, or applied to gene therapy, or given in a form added to something. Those used for such addition include polycations that act to neutralize the charge of phosphate backbone, such as polylysines, and hydrophobic ones such as lipids (e.g., phospholipids, cholesterols and the like) that enhance the interaction with cell membrane or increase nucleic acid uptake. Lipids preferred for addition are cholesterols and derivatives thereof (e.g., cholesteryl chloroformate, cholic acid and the like). These moieties may be attached to the 3′ end or 5′ end of a nucleic acid, and can also be attached via a base, sugar, or intramolecular nucleoside linkage. Other groups may be capping groups placed specifically at the 3′ end or 5′ end of the nucleic acid to prevent degradation by nucleases such as exonuclease and RNase. Such capping groups include, but are not limited to, hydroxyl protecting groups known in the art, including glycols such as polyethylene glycol and tetraethylene glycol.

[0042]

The inhibitory activities of these nucleic acids on the expression of the target protein can be examined using a transformant carrying the target gene, an in vivo and in vitro expression system for the target gene, or an in vivo or in vitro translation system for the target protein.

[0043]

A substance that inhibits the expression of the target protein in the present invention is not limited to the above-described nucleic acids comprising a base sequence complementary or substantially complementary to the base sequence of the mRNA encoding the target protein or a portion

thereof. As far as the substance directly or indirectly inhibits the production of the target protein, it may be other substance such as peptide, protein, organism-derived nonpeptidic compound (carbohydrates, lipid etc.), synthetic compound, microorganism culture, cell extract, plant extract, animal tissue extract and the like. These substances may be novel substances or known substances. Such a substance can be acquired by, for example, the screening method of the present invention described below.

[0044]

The "substance that inhibits activation of the target protein" in the present invention may be any as long as it inhibits a produced target protein from being present in an activated state, i.e., phosphorylated state, and divided into a substance that inhibits phosphorylation of a target protein and a substance that promotes dephosphorylation thereof. Examples of the former include, but are not limited to, a peptide to be, competitively with a target protein, a substrate for an enzyme that phosphorylates the target protein (e.g., a peptide to be a LIMK substrate competitively with cofilin, a peptide to be a PAK1 or ROCK1 or ROCK2 substrate competitively with LIMK, a peptide to be a Rac substrate competitively with PAK1, a peptide to be a Rho substrate competitively with ROCK1 or ROCK2 etc.) and the like, and examples of the latter include, but are not limited to, phosphatase that acts on a target protein (e.g., slingshot (ssh) that dephosphorylates cofilin etc.) and the like. Examples of the peptide to be, competitively with a target protein, a substrate for an enzyme that phosphorylates the target protein include a fragment thereof containing a target protein phosphorylation site (for example, Ser (third from the N terminal) for cofilin, etc.), which lacks a physiologically active domain of the target protein (actin polymerization activity etc. for cofilin, LIMK and cofilin activation (phosphorylation) activity etc. for PAK1, ROCK1, ROCK2 and

LIMK, and ROCK1 or ROCK2 activation (phosphorylation) activity for Rho, etc.) and the like. The phosphorylation site and physiologically active domain of the target protein of the present invention are known, and those of ordinary skill in the art can easily design or synthesize a peptide that can competitively act as a substrate (phosphoric acid group receptor) with the target protein, based on the information of the amino acid sequences (for example, SEQ ID NO: 2, 4, 6, 8, 10, 12, 14 or 16 for human) of cofilin, PAK1, LIMK, Rho, ROCK1 and ROCK2.

[0045]

In the present invention, "a substance that inhibits the action of the target protein of the present invention" may be any as long as it inhibits the target protein once produced functionally and activated (phosphorylated) from exhibiting its physiological activities (actin polymerization activity etc. for cofilin, LIMK and cofilin activation (phosphorylation) activity for PAK1 or ROCK1 or ROCK2 and LIMK, respectively, etc., ROCK1 or ROCK2 activation (phosphorylation) activity etc. for Rho); for example, a substance that inhibits dissociation of the phosphorylated cofilin from actin fiber, a substance that inhibits binding of PAK1 or ROCK1 or ROCK2 and LIMK to LIMK and cofilin and/or phosphorylation thereof, a substance that inhibits binding of Rho to ROCK1/2 and/or phosphorylation thereof and the like.

[0046]

Specifically, as an example of a substance that inhibits the action of the target protein (particularly Rho, ROCK1, ROCK2, PAK1 and LIMK) of the present invention, an antibody against said protein can be mentioned. The antibody may be a polyclonal antibody or a monoclonal antibody. These antibodies can be produced according to a method of antibody or antiserum production known per se. The isotype of the antibody is not particularly limited, and is preferably IgG, IgM or IgA, particularly preferably IgG. The antibody is not particularly

limited, as far as it has at least a complementarity determining region (CDR) for specifically recognizing and binding to a target antigen, and the antibody may be, in addition to a complete antibody molecule, for example, a fragment such as Fab, Fab', or $F(ab')_2$, a conjugate molecule prepared by a gene engineering technique, such as scFv, scFv-Fc, minibody, or diabody, or a derivative thereof modified with a molecule having protein-stabilizing action, such as polyethylene glycol (PEG).

In a preferred embodiment, the antibody against the target protein of the present invention is used as a medicament for a human recipient, the antibody (preferably monoclonal antibody) is an antibody having a reduced risk of exhibiting antigenicity when administered to humans, specifically a complete human antibody, a humanized antibody, a mouse-human chimera antibody or the like, and particularly preferably a complete human antibody. A humanized antibody and a chimera antibody can be prepared by gene engineering according to a conventional method. Although a complete human antibody can also be produced from a human-human (or mouse) hybridoma, it is desirable, for supplying a large amount of antibody stably and at low cost, that the antibody be produced using a human antibody-producing mouse or the phage display method.

[0047]

Since the target protein of the present invention is an intracellular signal transduction molecule constituting the cytoskeleton signaling cascade, a substance that inhibits the activity of said protein is desirably a substance of excellent entry into cells. Therefore, a more preferable substance that inhibits the action of the target protein of the present invention is a low-molecular compound that complies with Lipinski's Rule. Such a compound can be acquired by, for example, using the screening method of the present invention described below.

[0048]

Since a substance that inhibits expression, activation (phosphorylation) or action of the target protein of the present invention, namely, an inhibitor of the target protein of the present invention shows superior anticancer action such as cell proliferation suppressive effect and the like even on a trastuzumab resistant (low sensitive) cancer, it is useful for the prophylaxis and/or treatment of a HER2-expressing cancer, irrespective of the sensitivity against trastuzumab.

Therefore, a medicament containing one or more medicaments selected from the inhibitors of the target proteins of the present invention (cofilin, PAK1, LIMK, Rho, ROCK1, ROCK2) can be used as an agent for preventing or treating a trastuzumab-resistant (low sensitive) cancer and the like.

[0049]

In the present specification, cancer means a HER2 positive cancer, and refers to various carcinomas (particularly breast cancer (e.g., invasive ductal carcinoma, ductal cancer in situ, inflammatory breast cancer, etc.), prostate cancer (e.g., hormone-dependent prostate cancer, non-hormone dependent prostate cancer, etc.), pancreatic cancer (e.g., pancreatic duct cancer, etc.), gastric cancer (e.g., papillary adenocarcinoma, mucinous adenocarcinoma, adenosquamous cancer, etc.), lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, malignant mesothelioma, etc.), colon cancer (e.g., gastrointestinal stromal tumor, etc.), rectal cancer (e.g., gastrointestinal stromal tumor, etc.), colorectal cancer (e.g., familial colorectal cancer, hereditary nonpolyposis colorectal cancer, gastrointestinal stromal tumor, etc.), small intestinal cancer (e.g., non-Hodgkin lymphoma, gastrointestinal stromal tumor, etc.), esophagus cancer, duodenal cancer, cancer of tongue, pharyngeal cancer (e.g., nasopharyngeal carcinoma, oropharyngeal carcinoma, hypopharyngeal carcinoma, etc.),

salivary gland cancer, brain tumor (e.g., pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, etc.), schwannoma, liver cancer (e.g., primary liver cancer, extrahepatic bile duct cancer, etc.), kidney cancer (e.g., renal cell carcinoma, transitional cell cancer of renal pelvis and ureter, etc.), bile duct cancer, endometrial cancer, carcinoma of the uterine cervix, ovary cancer (e.g., ovarian epithelial cancer, extragonadal germ cell tumor, ovarian germ cell tumor, ovarial low malignant potential tumor, etc.), urinary bladder cancer, urethral cancer, skin cancer (e.g., ocular melanoma, Merkel cell carcinoma, etc.), Hemangioma, malignant lymphoma, malignant melanoma, thyroid cancer (e.g., medullary thyroid cancer, etc.), parathyroid cancer, nasal cancer, paranasal cancer, bone tumor (e.g., osteosarcoma, Ewing's tumor, uterus sarcoma, soft tissue sarcoma, etc.), vascular fibroma, retinoblastoma, penile cancer, testis tumor, solid cancer in childhood (e.g., Wilms' tumor, childhood kidney tumor, etc.), Kaposi's sarcoma, Kaposi's sarcoma related to AIDS, maxillary sinus tumor, fibrous histiocytoma, leiomyosarcoma, rhabdomyosarcoma, leukemia (e.g., acute myelocytic leukemia, acute lymphoblastic leukemia, etc.), etc.), and the like. It particularly refers to breast cancer, prostate cancer, gastric cancer, lung cancer, colon cancer, rectal cancer, colorectal cancer, esophagus cancer, pharyngeal cancer, ovary cancer, urinary bladder cancer and the like.

[0050]

(1) Medicament containing antisense nucleic acid, siRNA, or precursor nucleic acid thereof

A medicament comprising the above-mentioned nucleic acid comprising a base sequence complementary or substantially complementary to the base sequence of the mRNA of the target gene of the present invention or a portion thereof is of low toxicity, and can be administered as a liquid as it is, or as an appropriate dosage form of pharmaceutical composition, to

humans or non-human mammals (e.g., mice, rats, rabbits, sheep, pigs, bovines, cats, dogs, monkeys and the like) orally or parenterally (e.g., intravascular administration, subcutaneous administration and the like).

[0051]

When the nucleic acid of the present invention is used as an agent for preventing or treating cancer, the nucleic acid can be prepared and administered according to a method known per se. That is, the nucleic acid alone or after being functionally inserted into an appropriate expression vector for mammalian cells, such as a retrovirus vector, adenovirus vector, or adenovirus-associated virus vector, can be prepared according to a standard means. The nucleic acid can be administered as it is, or along with an auxiliary for promoting its uptake, using a gene gun or a catheter such as a hydrogel catheter. Alternatively, the nucleic acid can be prepared as an aerosol and topically administered into the trachea as an inhalant.

Furthermore, for the purpose of improving the disposition, extending the half-life, and increasing the intracellular uptake efficiency, the aforementioned nucleic acid may be prepared as a preparation (injection) alone or with a carrier such as a liposome, and administered intravenously, subcutaneously and the like.

[0052]

A nucleic acid of the present invention may be administered as it is, or as an appropriate pharmaceutical composition. The pharmaceutical composition used for administration may contain both a nucleic acid of the present invention and a pharmacologically acceptable carrier, diluent or excipient. Such a pharmaceutical composition is supplied in the form of a dosage form suitable for oral or parenteral administration.

[0053]

As examples of the composition for parenteral

administration, injections, suppositories and the like are used; the injections may include dosage forms such as intravenous injections, subcutaneous injections, intracutaneous injections, intramuscular injections and drip infusion injections. Such an injection can be prepared according to a publicly known method. An injection can be prepared by, for example, dissolving, suspending or emulsifying the above-described nucleic acid of the present invention in a sterile aqueous or oily solution in common use for injections. As examples of aqueous solutions for injection, physiological saline, an isotonic solution containing glucose or other auxiliary agent, and the like can be used, which may be used in combination with an appropriate solubilizer, for example, alcohol (e.g., ethanol), polyalcohol (e.g., propylene glycol, polyethylene glycol), non-ionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)] and the like. As examples of oily solutions, sesame oil, soybean oil and the like can be used, which may be used in combination with benzyl benzoate, benzyl alcohol and the like as solubilizers. The prepared injection solution is preferably filled in an appropriate ampoule. Suppositories used for rectal administration may be prepared by mixing the above-described nucleic acid in an ordinary suppository base.

[0054]

As the composition for oral administration, solid or liquid dosage forms, specifically tablets (including sugar-coated tables and film-coated tablets), pills, granules, powders, capsules (including soft capsules), syrups, emulsions, suspensions and the like can be mentioned. Such a composition is produced by a publicly known method, and may contain a carrier, diluent or excipient in common use in the field of pharmaceutical production. As examples of the carrier or excipient for tablets, lactose, starch, sucrose, magnesium stearate and the like can be used.

[0055]

The above-described pharmaceutical composition for parenteral or oral administration is conveniently prepared in a medication unit dosage form suitable for the dosage of the active ingredient. As examples of such a medication unit dosage form, tablets, pills, capsules, injections (ampoules), and suppositories can be mentioned. It is preferable that a nucleic acid of the present invention be contained at, for example, normally 5 to 500 mg, particularly 5 to 100 mg for injections, or 10 to 250 mg for other dosage forms, per medication unit dosage form.

[0056]

The dose of the above-described medicament containing the nucleic acid of the present invention varies depending on the subject of administration, target disease, symptoms, route of administration and the like; for example, when the medicament is used for the treatment/prevention of cancer of an adult, it is convenient to administer the nucleic acid of the present invention usually at about 0.01 to 20 mg/kg body weight, preferably about 0.1 to 10 mg/kg body weight, and more preferably about 0.1 to 5 mg/kg body weight, based on a single dose, about 1 to 5 times a day, preferably about 1 to 3 times a day, by intravenous injection. In the case of other modes of parenteral administration and oral administration, similar doses may be administered. In case the symptom is particularly severe, the dose may be increased according to the symptom.

[0057]

Each of the aforementioned compositions may comprise any other active ingredient that does not produce an unwanted interaction when formulated with a nucleic acid of the present invention.

[0058]

(2) Medicament containing peptide, phosphatase, antibody and the like

A medicament containing the aforementioned peptide,

phosphatase etc. that inhibit presence of the target protein of the present invention in an activated (phosphorylated) state, or an antibody against the target protein (particularly human antibody, humanized antibody etc.) is of low toxicity, and can be administered as a liquid as it is, or as an appropriate dosage form of pharmaceutical composition, to humans or mammals (e.g., mice, rats, rabbits, sheep, pigs, bovines, cats, dogs, monkeys and the like) orally or parenterally (e.g., intravascular administration, subcutaneous administration and the like).

[0059]

The above-described peptide, phosphatase, antibody and the like may be administered as it is, or as an appropriate pharmaceutical composition. The pharmaceutical composition used for administration may contain both the above-described peptide, phosphatase, antibody and the like, and a pharmacologically acceptable carrier, diluent or excipient. Such a pharmaceutical composition is provided as a dosage form suitable for oral or parenteral administration.

[0060]

As examples of the composition for parenteral administration, injections, suppositories and the like are used; the injections may include dosage forms such as intravenous injections, subcutaneous injections, intracutaneous injections, intramuscular injections, and drip infusion injections. Such an injection can be prepared according to a commonly known method. An injection can be prepared by, for example, dissolving, suspending or emulsifying the above-described peptide, phosphatase, antibody and the like in a sterile aqueous or oily solution in common use for injections. As examples of aqueous solutions for injection, physiological saline, an isotonic solution containing glucose or other auxiliary agent and the like can be used, which may be used in combination with an appropriate solubilizer, for example, an alcohol (e.g., ethanol), a

polyalcohol (e.g., propylene glycol, polyethylene glycol), a non-ionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)] and the like. As examples of oily solutions, sesame oil, soybean oil and the like can be used, which may be used in combination with solubilizers such as benzyl benzoate, benzyl alcohol. The injection solution prepared is preferably filled in an appropriate ampoule. Suppositories used for rectal administration may be prepared by mixing the above-described peptide, phosphatase, antibody and the like in an ordinary suppository base.

[0061]

For example, the composition for oral administration includes solid or liquid preparations, specifically, tablets (including sugar-coated tables and film-coated tablets), pills, granules, powder, capsules (including soft capsules), syrup, emulsions, suspensions, etc. Such a composition is manufactured by publicly known methods and may contain a carrier, a diluent or excipient conventionally used in the field of pharmaceutical preparations. Examples of the carrier or excipient for tablets are lactose, starch, sucrose, magnesium stearate, etc.

[0062]

Advantageously, the pharmaceutical compositions for parenteral or oral administration described above are prepared into a medication unit dosage form suited to fit a dose of the active ingredients. Such a medication unit dosage form includes, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc. It is preferable that the antibody be contained normally at 5 to 500 mg, particularly 5 to 100 mg for injections, or 10 to 250 mg for other dosage forms, per medication unit dosage form.

[0063]

The dose of the above-described medicament containing the above-described peptide, phosphatase, antibody and the like

varies depending on the subject of administration, target disease, symptoms, route of administration and the like; for example, when the medicament is used for the treatment/prevention of cancer in an adult, it is convenient to administer the peptide, phosphatase, antibody and the like usually at about 0.01 to 20 mg/kg body weight, preferably about 0.1 to 10 mg/kg body weight, and more preferably 0.1 to 5 mg/kg body weight, based on a single dose, about 1 to 5 times a day, preferably about 1 to 3 times a day, by intravenous injection. In the case of other parenteral administrations and oral administration, a similar dose can be administered. If the symptom is particularly severe, the dosage may be increased depending on the symptom.

[0064]

The above-described peptide, phosphatase, antibody and the like can be administered as it is, or as an appropriate pharmaceutical composition. The pharmaceutical composition used for the above-described administration contains both the above-described antibody and a pharmacologically acceptable carrier, diluent or excipient. Such a composition is supplied in the form of a dosage form suitable for oral or parenteral administration (e.g., intravascular injection, subcutaneous injection and the like).

Each of the aforementioned compositions may comprise any other active ingredient that does not produce an unwanted interaction when formulated with the above-described peptide, phosphatase, antibody and the like.

[0065]

Moreover, used in the present invention one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor can be screened for by the following screening method. A preferable embodiment of the screening method of the present invention is a method including evaluating the cytoskeleton signal transduction

inhibitory activity of a test compound and selecting a compound having a cytoskeleton signal transduction inhibitory activity. The cytoskeleton signal transduction inhibitory activity means an activity that can inhibit signal transduction via a protein involved in cytoskeleton signal transduction by expression inhibitory, activation inhibitory, destabilization and the like of the protein involved in the cytoskeleton signal transduction. Therefore, the cytoskeleton signal transduction inhibitory activity can be evaluated based on the inhibitory activity against cytoskeleton signal transduction. The thus-selected compound suppresses the activity of cofilin, which is a downstream molecule, and becomes a candidate compound as an agent for the treatment or prophylaxis of a trastuzumab-resistant cancer.

[0066]

The expression inhibitory activity, activation inhibitory activity, destabilization activity and the like of a protein involved in the cytoskeleton signal transduction can be measured according to a known method. Specifically, for example, the cytoskeleton signal transduction inhibitory activity can be evaluated by measuring the PAK1 inhibitory activity, Rho inhibitory activity, ROCK inhibitory activity, LIMK inhibitory activity and the like. Here, the PAK1 inhibitory activity, Rho inhibitory activity, ROCK inhibitory activity, LIMK inhibitory activity or cofilin inhibitory activity means an activity that can inhibit signal transduction via PAK1 protein, Rho protein, ROCK protein, LIMK protein or cofilin protein by expression inhibition, activation inhibition, inactivation and the like of PAK1 protein, Rho protein, ROCK protein or LIMK protein.

[0067]

The PAK inhibitory activity can be measured, for example, by modifying the measurement experiment of LIMK activation by PAK1 described in Nat Cell Biol. (1999) 1, 253-259, performing the experiment using a test substance, and considering the

activation inhibitory rate. The Rho inhibitory activity can be measured, for example, by the method described in Journal of Neurochemistry (2002) 81, 9-16. The ROCK inhibitory activity can be measured, for example, by the method described in Biochem. J. (2000) 351, 95-105. The LIMK inhibitory activity can be measured, for example, by modifying the measurement experiment of kinase activity of LIMK described in Nature (1998) 393, 809-812 or Biochem. J. (1999) 343, 99-105, performing the experiment using a test substance, and considering the activation inhibitory rate.

[0068]

As examples of test compounds, peptides, proteins, antibodies, non-peptide compounds, synthetic compounds, fermentation products, cell extracts, plant extracts, animal tissue extracts, plasma and the like can be mentioned; these compounds may be novel or publicly known. The test compound may form a salt, and as a salt of the test compound, a physiologically acceptable metal salt, an ammonium salt, a salt with an organic base, a salt with an inorganic acid, a salt with an organic acid, a salt with a basic or acidic amino acid and the like can be mentioned. Preferable examples of the metal salt include alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt, barium salt and the like; aluminum salt and the like. Preferable examples of the salt with organic base include salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like. Preferable examples of the salt with inorganic base include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like. Preferable examples of the salt with organic acid include salts with formic acid, acetic acid, trifluoroacetic acid, propionic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid,

maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzoic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like. Preferable examples of the salt with basic amino acid include salts with arginine, lysine, ornithine and the like, and preferable examples of the salt with acidic amino acid include salts with aspartic acid, glutamic acid and the like.

[0069]

More specifically, for example, provided are

(1) a method of screening for a cofilin inhibitor, a PAK inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor, or a ROCK2 inhibitor, comprising comparing the cytoskeleton signal transduction activity of a cell between (i) when the test compound is contacted with the cell, and (ii) when the test compound is not contacted with the cell,

(2) a method of screening for a cofilin inhibitor, a PAK inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor, or a ROCK2 inhibitor, comprising comparing the expression levels of a gene encoding a protein involved in the cytoskeleton signal transduction such as PAK1 protein, Rho protein, ROCK protein, LIMK protein, cofilin protein and the like of a cell between (i) when the test compound is contacted with the cell, and (ii) when the test compound is not contacted with the cell,

(3) a method of screening for a cofilin inhibitor, a PAK inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor, or a ROCK2 inhibitor, comprising comparing the activity of a protein involved in the cytoskeleton signal transduction such as PAK1 protein, Rho protein, ROCK protein, LIMK protein, cofilin protein and the like between (i) in the presence of the test compound, and (ii) in the absence of the test compound,

(4) a method of screening for a cofilin inhibitor, a PAK inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor, or a ROCK2 inhibitor, comprising comparing the

stability of a protein involved in the cytoskeleton signal transduction such as PAK1 protein, Rho protein, ROCK protein, LIMK protein, cofilin protein and the like between (i) in the presence of the test compound, and (ii) in the absence of the test compound.

[0070]

(1) Method of screening for a cofilin inhibitor, a PAK inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor, or a ROCK2 inhibitor, comprising comparing the cytoskeleton signal transduction activity of a cell between (i) when the test compound is contacted with the cell, and (ii) when the test compound is not contacted with the cell

In this method, a test compound is first contacted with the cell expressing a protein involved in the cytoskeleton signal transduction. The derivation of the "cells" to be used may be, but is not limited to, cells derived from human, mouse, cat, dog, bovine, sheep, bird and the like. As the "cell expressing a protein involved in the cytoskeleton signal transduction", a cell expressing a protein involved in the cytoskeleton signal transduction, or a cell into which an exogenous gene encoding a protein involved in the cytoskeleton signal transduction has been introduced, and in which the gene is expressed can be utilized. The cell in which an exogenous gene encoding a protein involved in the cytoskeleton signal transduction is expressed can be generally produced by introducing, into a host cell, an expression vector inserted with a gene encoding a protein involved in the cytoskeleton signal transduction. The expression vector can be produced by a general genetic engineering technique.

[0071]

Next, the cytoskeleton signal transduction activity (e.g., phosphorylation activity) is measured. Specifically, for example, in (i) and (ii), the above-mentioned cell is cultured, and the cytoskeleton signal transduction activity thereof is measured. The cytoskeleton signal transduction activity can be

measured by a known method, for example, by measuring the phosphorylation of Rac, PAK1, Rho, ROCK1, ROCK2 or LIMK, Western blotting or ELISA using a phosphorylation antibody that specifically reacts with those proteins, or phosphorylation of cofilin downstream thereof by western blotting or ELISA using a phosphorylation antibody that specifically reacts with those proteins and the like. As the test compound, those similar to the aforementioned can be used.

[0072]

Then, a compound that suppresses (decreases) cytoskeleton signal transduction as compared to the absence of contact with the test compound (control) is selected. For example, a test compound that suppresses the cytoskeleton signal transduction activity in the above-mentioned (i) by about 20% or above, preferably 30% or above, more preferably about 50% or above, as compared to that in the above-mentioned (ii) can be selected as a compound that suppresses (decreases) cytoskeleton signal transduction. The thus-selected compound suppresses the activity of cofilin, which is a downstream molecule, and becomes a candidate compound as an agent for the treatment or prophylaxis of cancer.

[0073]

(2) A method of screening for a cofilin inhibitor, a PAK inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor, or a ROCK2 inhibitor, comprising comparing the expression levels of a gene encoding a protein involved in the cytoskeleton signal transduction such as PAK1 protein, Rho protein, ROCK protein, LIMK protein, cofilin protein and the like of a cell between (i) when the test compound is contacted with the cell, and (ii) when the test compound is not contacted with the cell

In this method, in the same manner as above, a test compound is first contacted with a cell that expresses a gene encoding a protein involved in the cytoskeleton signal transduction. As the cell, a cell that expresses a gene

encoding a protein involved in the cytoskeleton signal transduction, such as PAK1 protein, Rho protein, ROCK protein, LIMK protein, cofilin protein and the like, is preferably used, for example, human vulva cancer cell A431, human large intestine cancer cells HCT-15, SW620, human breast cancer cells BT-474, SK-Br-3, MCF-7, MDA-MB-231, human non-small cell lung cancer cell A549, human ovary cancer cell SK-OV-3 and the like.

[0074]

Next, the expression of a gene encoding a protein involved in the cytoskeleton signal transduction is measured. Specifically, for example, in (i) and (ii), the above-mentioned cell is cultured, and the expression level of a gene encoding a protein involved in the cytoskeleton signal transduction is measured. The expression level of a gene can be measured by measuring the transcription level or translation level and the like by a known method. For example, the transcription level of the gene can be measured by extracting mRNA from a cell that expresses a gene encoding a protein involved in the cytoskeleton signal transduction by a conventional method, and performing Northern hybridization or RT-PCR using the mRNA as a template. Alternatively, a promoter region of a gene encoding a protein involved in the cytoskeleton signal transduction is isolated by a conventional method, a marker gene (e.g., gene detectable with luminescence, fluorescence, color development and the like of luciferase, GFP, galactosidase and the like as indices can be nonlimitatively mentioned) is ligated downstream thereof, and the activity of the marker gene is observed, whereby the transcription level of the gene can be measured. In addition, a protein fraction is recovered from a cell that expresses a gene encoding a protein involved in the cytoskeleton signal transduction, and the expression of a protein involved in cytoskeleton signal transduction is detected by electrophoresis such as SDS-PAGE and the like, whereby the

translation level of the gene can also be measured. Furthermore, it is possible to measure the translation level of a gene by performing Western blotting using an antibody against a protein involved in the MAPK signal transduction and detecting the protein expression. The antibody to be used for the detection of a protein involved in the cytoskeleton signal transduction is not particularly limited as long as it can be detected, and, for example, both a monoclonal antibody and a polyclonal antibody can be used. As the test compound, those similar to the above are used.

[0075]

Then, a compound that suppresses (decreases) the expression level of a gene encoding a protein involved in the cytoskeleton signal transduction as compared to the absence of contact with a test compound (control) is selected. The thus-selected compound suppresses the activity of cofilin, which is a downstream molecule, and becomes a candidate compound as an agent for the treatment or prophylaxis of cancer.

[0076]

(3) Method of screening for a cofilin inhibitor, a PAK inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor, or a ROCK2 inhibitor, comprising comparing the activity of a protein involved in the cytoskeleton signal transduction such as PAK1 protein, Rho protein, ROCK protein, LIMK protein, cofilin protein and the like between (i) in the presence of the test compound, and (ii) in the absence of the test compound

For example, in (i) and (ii) above, the activity of a protein involved in the cytoskeleton signal transduction such as PAK1 protein, Rho protein, ROCK protein, LIMK protein, cofilin protein and the like is measured. Then, a compound that suppresses (decreases) the activity of a gene encoding a protein involved in the cytoskeleton signal transduction as compared to the absence of a test compound (control) is selected. The activity of a protein involved in the

cytoskeleton signal transduction can be measured by a known method, for example, by measuring the phosphorylation of Rac, PAK1, Rho, ROCK1, ROCK2 or LIMK, Western blotting or ELISA using a phosphorylation antibody that specifically reacts with those proteins, or phosphorylation of cofilin downstream thereof by Western blotting or ELISA using a phosphorylation antibody that specifically reacts with those proteins and the like. As the test compound, those similar to the aforementioned can be used. The thus-selected compound suppresses the activity of cofilin, which is a downstream molecule, and becomes a candidate compound as an agent for the treatment or prophylaxis of cancer.

[0077]

(4) Method of screening for a cofilin inhibitor, a PAK inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor, or a ROCK2 inhibitor, comprising comparing the stability of a protein involved in the cytoskeleton signal transduction such as PAK1 protein, Rho protein, ROCK protein, LIMK protein, cofilin protein and the like between (i) in the presence of the test compound, and (ii) in the absence of the test compound.

In (i) and (ii) above, the stability of a protein involved in the cytoskeleton signal transduction is measured. The stability of a protein involved in the cytoskeleton signal transduction can be measured by a known method, for example, the method described in Cancer Res. 65: 596-604 (2005) (^{35}S-labelled pulse chase method) and the like. Then, a compound that suppresses (decreases) the stability of a protein involved in the cytoskeleton signal transduction as compared to the absence of a test compound (control) is selected. The thus-selected compound suppresses the activity of cofilin, which is a downstream molecule, and becomes a candidate compound as an agent for the treatment or prophylaxis of cancer.

[0078]

The compound selected by the above-mentioned methods is preferably screened for using suppression of the phosphorylation level of cofilin protein, which is a downstream molecule, as an index. For example, PAK1 inhibitor, LIMK inhibitor, Rho inhibitor, ROCK1 inhibitor or ROCK2 inhibitor is preferably screened for based on the comparison of the phosphorylation of the cofilin protein in the cell between (i) with a cell treatment with a test compound and (ii) without a cell treatment with a test compound.

[0079]

Specifically, for example, in the above-mentioned (i) and (ii), the above-mentioned cells are cultured, and the phosphorylation level of the cofilin protein thereof is measured. The phosphorylation level of the cofilin protein can be measured by a known method such as Westernblot or ELISA/EIA and the like. For example, the above-mentioned cells are cultured and lysed, and Westernblot or ELISA/EIA using an antibody against phosphorylated cofilin is performed to detect the phosphorylation level of the protein, whereby the suppressive activity on the kinase activity can be measured. The antibody to be used for the detection of phosphorylated cofilin is not particularly limited as long as it can be detected, and, for example, both a monoclonal antibody and a polyclonal antibody can be used. As the test compound, one selected by the above-mentioned method is used.

[0080]

Then, a compound that suppresses (decreases) the phosphorylation level of cofilin protein as compared to the absence of contact with a test compound (control) is selected. The thus-selected compound suppresses the activity of cofilin, which is a downstream molecule, and becomes a candidate compound as an agent for the treatment or prophylaxis of cancer.

[0081]

The cofilin, PAK1, LIMK, Rho, ROCK1 or ROCK2 inhibitor

obtained using the above-mentioned screening methods can be formulated into a preparation as an agent for preventing or treating cancer by a conventional method such as blending, kneading, granulation, tabletting, coating, sterilization treatment, emulsification and the like according to the preparation form. For production of the preparation, for example, each section of the Japanese Pharmacopoeia Preparation General Rules and the like can be referred to. In addition, the agent for preventing or treating cancer of the present invention may be formed into a sustained-release preparation containing the active ingredient and a biodegradable polymer compound. The sustained-release preparation can be formulated by the method described in JP-A-9-263545.

While the content of one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor in the agent for preventing or treating cancer of the present invention varies depending on the preparation form, it is generally about 0.01 - 100 wt%, preferably about 0.1 - 50 wt%, more preferably about 0.5 - 20 wt%, relative to the whole preparation.

When one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor are used as an agent for preventing or treating cancer, they can be administered orally or parenterally as they are, or in the form of a solid agent such as powder, fine granules, granules, tablet, capsule and the like or a liquid such as injection and the like by mixing with an appropriate pharmaceutically acceptable carrier, such as excipient (e.g., starch, lactose, sucrose, calcium carbonate, calcium phosphate and the like), binder (e.g., starch, gum arabic, carboxymethylcellulose, hydroxypropylcellulose, crystalline cellulose, alginic acid, gelatin, polyvinylpyrrolidone and the like), lubricant (for

example, stearic acid, magnesium stearate, calcium stearate, talc and the like), disintegrant (e.g., calcium carboxymethylcellulose, talc and the like), diluent (e.g., water for injection, saline and the like), additive (stabilizer, preservative, colorant, flavor, dissolution aid, emulsifier, buffer agent, isotonicity agent and the like) as necessary and the like by a conventional method.

The content of the carrier in the agent for preventing or treating cancer of the present invention is generally about 0 - 99.9 wt%, preferably about 10 - 99.9 wt%, more preferably about 10 - 90 wt%, relative to the whole preparation.

While the dose varies depending on the kind of one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor, level of symptoms, age, sex, body weight and difference in the sensitivity of the subject of administration, timing of administration, administration route, administration intervals, properties, dosage form and kind of a formulated pharmaceutical composition, and the like, for oral administration to an adult patient with breast cancer, for example, it is about 0.005 - 100 mg, preferably about 0.05 - 50 mg, more preferably about 0.2 - 30 mg, of the substance of the present invention per kg body weight per day in one to 3 portions.

When the agent for preventing or treating cancer of the present invention is a sustained-release preparation, the dose varies depending on the kind and content of one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor, dosage form, duration of drug release, animal as subject of administration (e.g., mammals such as human, rat, mouse, cat, dog, rabbit, bovine, swine and the like), and administration object. When applied, for example, by parenteral administration, about 0.1 mg to about 100 mg of one or more medicaments selected from a cofilin

inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor only needs to be released from the administered preparation in one week.

[0082]

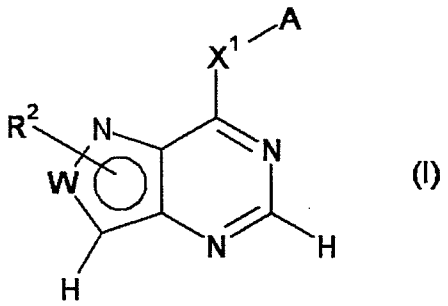
Since activation of cofilin is considered to provide cancer cells with resistance to trastuzumab, conventional HER2 inhibitors can be effectively used for the prophylaxis or treatment of a trastuzumab-resistant cancer by using a direct or indirect cofilin inhibitor (e.g., cofilin inhibitor, PAK1 inhibitor, LIMK inhibitor, Rho inhibitor, ROCK1 inhibitor or ROCK2 inhibitor) together with a conventional HER2 inhibitor.

Examples of the conventional HER2 inhibitor include anti-HER2 antibody (e.g., trastuzumab (herceptin (trademark))), Lapatinib (GW572016) and the like.

[0083]

As other conventional HER2 inhibitor, a compound represented by the formula (I):

[0084]



(I)

[0085]

wherein W is $C(R^1)$ or N,

A is an optionally substituted aryl group or an optionally substituted heteroaryl group,

X^1 is $-NR^3-Y^1-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-CHR^3-$

wherein R^3 is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or R^3 is optionally bonded to a carbon atom or a hetero atom on the aryl group or the heteroaryl group represented by A to form an optionally substituted ring structure, and

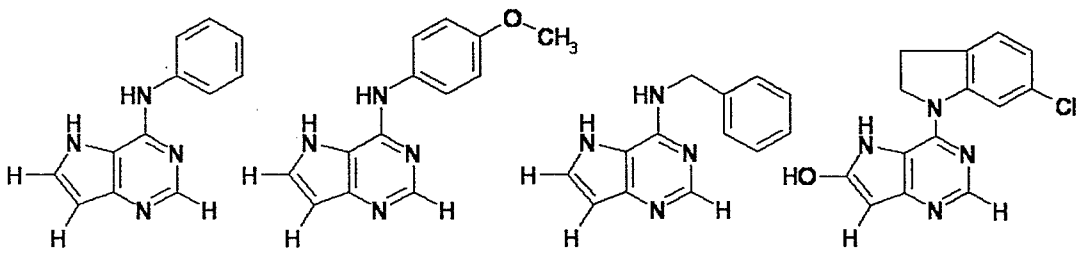
Y^1 is a single bond or an optionally substituted C_{1-4} alkylene

or an optionally substituted -O-(C_{1-4} alkylene)-,

R^1 is a hydrogen atom or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom, and R^2 is a hydrogen atom or an optionally substituted group bonded via a carbon atom or a sulfur atom, or

R^1 and R^2, or R^2 and R^3 are optionally bonded to form an optionally substituted ring structure, provided that the compounds represented by the formulas

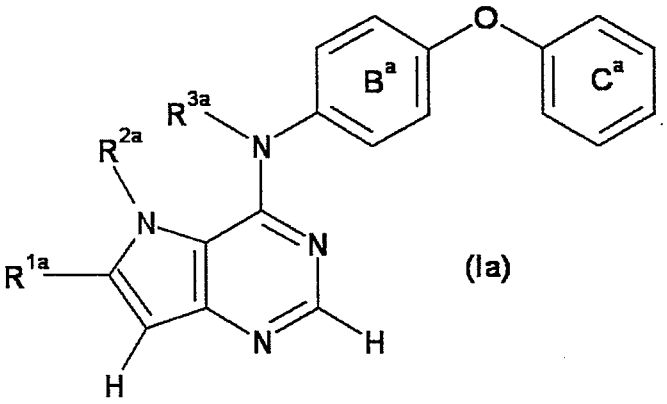
[0086]



[0087]

are excluded, or a salt thereof is used, and more preferably, a compound represented by the formula (Ia):

[0088]



[0089]

wherein R^{1a} is a hydrogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

R^{2a} is a hydrogen atom, or an optionally substituted group bonded via a carbon atom or a sulfur atom, or

R^{1a} and R^{2a}, or R^{2a} and R^{3a} are optionally bonded to each other to form an optionally substituted ring structure,

R^{3a} is a hydrogen atom or an optionally substituted aliphatic

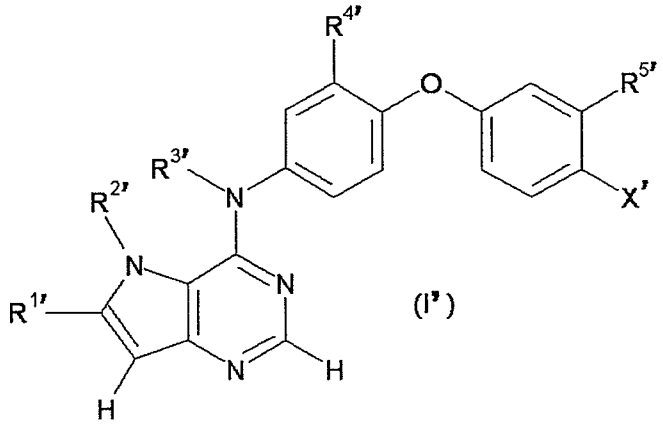
hydrocarbon group, or R^{3a} is optionally bonded via a carbon atom of the adjacent phenyl group to form an optionally substituted ring structure,

B^a is an optionally substituted benzene ring, and C^a is an optionally substituted C_{6-18} aryl group, or a salt thereof is used.

[0090]

As a still other conventional HER2 inhibitor, a compound represented by the formula (I'):

[0091]



(I')

[0092]

wherein

$R^{1'}$ is a hydrogen atom,

$R^{2'}$ is a C_{1-6} alkyl group substituted by a group represented by $-NR^{6'}-CO-(CH_2)_n-SO_2-$(optionally halogenated C_{1-4} alkyl) wherein n is an integer of 1 to 4, $R^{6'}$ is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

$R^{3'}$ is a hydrogen atom or a C_{1-6} alkyl group,

$R^{4'}$ is a halogen atom or a C_{1-6} alkyl group,

$R^{5'}$ is a halogen atom or a C_{1-6} alkyl group, or

X' is a hydrogen atom or a halogen atom,

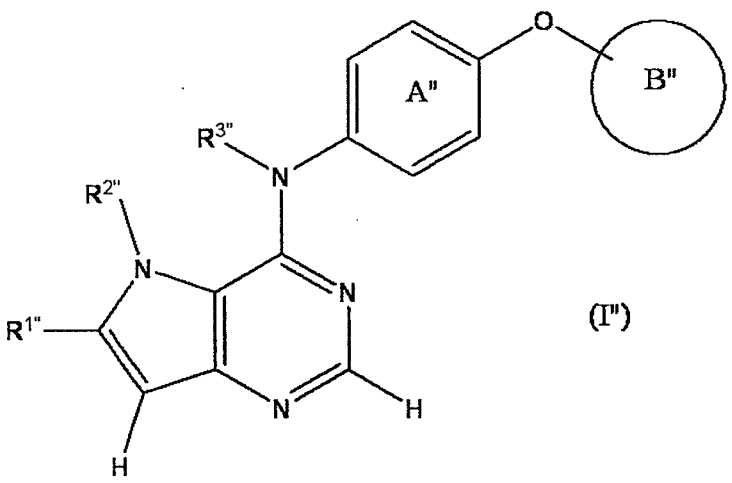
or a salt thereof, excluding N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide, is used.

[0093]

As a yet other conventional HER2 inhibitor, a compound

represented by the formula (I″):

[0094]



(I″)

[0095]

wherein

$R^{1''}$ is a hydrogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

$R^{2''}$ is a hydrogen atom, or an optionally substituted group bonded via a carbon atom or a sulfur atom,

or, $R^{1''}$ and $R^{2''}$, or $R^{2''}$ and $R^{3''}$ are optionally bonded to each other to form an optionally substituted ring structure;

$R^{3''}$ is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group,

or $R^{3''}$ is optionally bonded to a carbon atom of ring A″ to form an optionally substituted ring structure;

ring A″ is an optionally substituted benzene ring;

ring B″ is (i) an optionally substituted fused ring, or

(ii) a pyridine ring having optionally substituted carbamoyl wherein the pyridine ring is optionally further substituted;

or a salt thereof is used.

[0096]

The compounds of the formula (I) and the formula (Ia) (hereinafter sometimes to be abbreviated as compound (I) and compound (Ia), respectively, or simply referred to as compound (I)) are explained in the following.

[0097]

In compound (I), unless otherwise specified, the "aryl" in the "aryl group" and the substituents includes a monocyclic aryl group and a fused polycyclic aryl group. As the "aryl group", for example, a C_{6-18} aryl group can be mentioned. As the "C_{6-18} aryl group", for example, phenyl, biphenylyl, naphthyl, anthryl, phenanthryl and acenaphthylenyl can be mentioned.

[0098]

In compound (I), as the "heterocyclic group" (and "heterocyclyl-" in the substituents), for example, a 5- to 8-membered heteroaryl group or a 5- to 8-membered saturated or unsaturated aliphatic heterocyclic group containing, as an atom constituting a ring system (ring atom), one or more (preferably 1 to 4, more preferably 1 or 2) hetero atoms selected from an oxygen atom, an optionally oxidized sulfur atom and a nitrogen atom and the like (preferably, an oxygen atom, a sulfur atom and a nitrogen atom etc.) can be mentioned.

[0099]

In compound (I), unless otherwise specified, as the "aliphatic hydrocarbon group", a straight chain or branched aliphatic hydrocarbon group having 1 to 15 carbon atoms (preferably, 1 to 8 carbon atoms) can be mentioned. As such "aliphatic hydrocarbon group", for example, a C_{1-8} alkyl group, a C_{2-8} alkenyl group, a C_{2-8} alkynyl group, a C_{3-8} cycloalkyl group and the like can be mentioned.

[0100]

In compound (I), unless otherwise specified, as the "heteroaryl group", an monocyclic aromatic heterocyclic group (e.g., 5- or 6-membered monocyclic aromatic heterocyclic group such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl and the like)

and an aromatic fused heterocyclic group (e.g., 8- to 12-membered aromatic fused heterocyclic group such as benzofuranyl, isobenzofuranyl, benzothienyl, indolyl, isoindolyl, 1H-indazolyl, benzindazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, benzopyranyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl and the like) and the like can be mentioned. As the aromatic fused heterocyclic group, a heterocycle wherein the aforementioned 5- or 6-membered monocyclic aromatic heterocyclic group is fused with a benzene ring and a heterocycle wherein the same or different two heterocycles of the aforementioned 5- or 6-membered monocyclic aromatic heterocyclic group are fused are preferable.

[0101]

In compound (I), unless otherwise specified, as the "aliphatic heterocyclic group", for example, a 3- to 8-membered (preferably 5- or 6-membered) saturated or unsaturated (preferably saturated) aliphatic heterocyclic group such as oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, dihydro-1,2,4-oxadiazolyl and the like, and the like can be mentioned.

[0102]

In compound (I), unless otherwise specified, as the "C_{1-8} alkyl group", for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-

pentyl, neopentyl, n-hexyl, i-hexyl, n-heptyl and n-octyl and the like can be mentioned, with preference given to a C_{1-6} alkyl group. In compound (I), moreover, unless otherwise specified, as the "C_{1-4} alkyl group", for example, methyl, ethyl, n-propyl, i-propyl, n-butyl and i-butyl can be mentioned.

[0103]

In compound (I), unless otherwise specified, as the "C_{2-8} alkenyl group", for example, vinyl, (1- or 2-)propenyl, (1-, 2- or 3-)butenyl, pentenyl, octenyl and (1,3-)butadienyl can be mentioned, with preference given to a C_{2-4} alkenyl group.

[0104]

In compound (I), unless otherwise specified, as the "C_{2-8} alkynyl group", for example, ethynyl, (1- or 2-)propynyl, (1-, 2- or 3-)butynyl, pentynyl and octynyl can be mentioned, with preference given to a C_{2-4} alkynyl group.

[0105]

In compound (I), unless otherwise specified, as the "C_{3-8} cycloalkyl group", for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl can be mentioned, with preference given to a C_{3-6} cycloalkyl group.

[0106]

In compound (I), unless otherwise specified, as the "C_{1-4} alkylene", for example, methylene, ethylene, trimethylene, tetramethylene and propylene and the like can be mentioned.

[0107]

In compound (I), unless otherwise specified, as the "-O-(C_{1-4} alkylene)-", for example, $-OCH_2-$, $-OCH_2CH_2-$, $-O(CH_2)_3-$, $-O(CH_2)_4-$, $-OCH(CH_3)-$, $-OC(CH_3)_2-$, $-OCH(CH_3)CH_2-$, $-OCH_2CH(CH_3)-$, $-OC(CH_3)_2CH_2-$ and $-OCH_2C(CH_3)_2-$ and the like can be mentioned.

[0108]

In compound (I), unless otherwise specified, as the "C_{6-18} aryl-carbonyl group", for example, benzoyl, naphthoyl, anthrylcarbonyl, phenanthrylcarbonyl and acenaphthylenylcarbonyl and the like can be mentioned.

[0109]

In compound (I), unless otherwise specified, as the "C_{6-18} aryl-C_{1-4} alkyl-carbonyl group", for example, benzylcarbonyl, 3-phenylpropionyl, 2-phenylpropionyl, 4-phenylbutyryl and 5-phenylpentanoyl and the like can be mentioned.

[0110]

In compound (I), unless otherwise specified, as the "halogen", fluorine, chlorine, bromine and iodine can be mentioned.

[0111]

As the "5- to 8-membered heterocyclyl-carbonyl group containing 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom", "a 5- to 8-membered cyclic amino-carbonyl group optionally having 1 or 2 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom" is preferable, for example, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, piperazin-1-ylcarbonyl, morpholin-4-ylcarbonyl, thiomorpholin-4-ylcarbonyl and the like can be mentioned.

[0112]

In the above-mentioned formula, as the "aryl group" for A, a C_{6-18} aryl group is preferable, and phenyl is more preferable.

[0113]

The "aryl group" for A is optionally substituted by a group represented by the formula $-Y^2-B$ wherein Y^2 is a single bond, -O-, -O-(C_{1-3} alkylene)- (preferably $-OCH_2-$), -NH- or -S-, and B is an aryl group, a heterocyclic group, a C_{3-8} cycloalkyl group, a carbamoyl group, a ureido group, a C_{6-18} aryl-carbonyl group or a C_{6-18} aryl-C_{1-4} alkyl-carbonyl group, each of which is optionally substituted.

[0114]

As Y^2, a single bond, -O- or $-OCH_2-$ is preferable, and -O- or $-OCH_2-$ is more preferable.

[0115]

As the "aryl group" for B, a C_{6-18} aryl group is

preferable, and phenyl is more preferable.

[0116]

As the "heterocyclic group" for B, the aforementioned "5- or 6-membered monocyclic aromatic heterocyclic group" is preferable, and pyridyl is more preferable.

[0117]

The "aryl group", "heterocyclic group", "C_{6-18} aryl-carbonyl group" or "C_{6-18} aryl-C_{1-4} alkyl-carbonyl group" for B may have, for example, 1 to 5, the same or different substituents selected from halogen, optionally halogenated C_{1-4} alkyl, hydroxy, optionally halogenated C_{1-4} alkyloxy, C_{1-4} alkyloxymethyl, hydroxyl-C_{1-4} alkyl, C_{1-4} alkyl-carbonyl, carboxy, C_{1-4} alkoxy-carbonyl, cyano, carbamoyl, sulfamoyl, nitro, amino, C_{1-4} alkyl-carbonylamino, C_{1-4} alkoxy-carbonylamino and C_{1-4} alkyl-sulfonylamino, at any substitutable position(s).

[0118]

The "aryl group" for A may further have, besides the above-mentioned group represented by the formula $-Y^2-B$, 1 to 5, the same or different substituents at substitutable optional position(s). As such substituent, substituents similar to those exemplified for the "aryl group" or "heterocyclic group" for B can be mentioned.

[0119]

As the "aliphatic hydrocarbon group" for R^3, a C_{1-8} alkyl group, a C_{2-8} alkenyl group, a C_{2-8} alkynyl group and a C_{3-8} cycloalkyl group are preferable.

[0120]

The "aliphatic hydrocarbon group" for R^3 is optionally substituted by 1 to 3 substituents selected from halogen, hydroxy, C_{1-4} alkyloxy, C_{1-4} alkyl-carbonyl, carboxy, C_{1-4} alkoxy-carbonyl, cyano, carbamoyl, sulfamoyl, nitro, amino, C_{1-4} alkyl-carbonylamino, C_{1-4} alkoxy-carbonylamino and C_{1-4} alkyl-sulfonylamino.

[0121]

The "C_{1-4} alkylene" and "-O-(C_{1-4} alkylene)-" for Y^1 are

optionally substituted by 1 to 3 substituents selected from halogen, hydroxy, C_{1-4} alkyloxy, C_{1-4} alkyl-carbonyl, carboxy, C_{1-4} alkoxy-carbonyl, cyano, carbamoyl, sulfamoyl, nitro, amino, C_{1-4} alkyl-carbonylamino, C_{1-4} alkoxy-carbonylamino and C_{1-4} alkyl-sulfonylamino.

[0122]

As X^1, $-NR^3-$ wherein R^3 is as defined above is preferable.

[0123]

As the "optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom" for R^1, a group of the formula $-X^2-R^4$ can be mentioned, wherein X^2 is a single bond, -NH- or -O-, and R^4 is a hydrogen atom, a cyano group, or a C_{1-8} alkyl group, a C_{2-8} alkenyl group, a C_{2-8} alkynyl group, a carbamoyl group, a C_{1-8} alkyl-carbonyl group, a C_{3-8} cycloalkyl group, a C_{6-18} aryl group, a C_{6-18} aryl-C_{1-4} alkyl group, a C_{6-18} aryl-carbonyl group, a C_{6-18} aryl-C_{1-4} alkyl-carbonyl group, a heterocyclic group, a heterocyclyl-C_{1-4} alkyl group, a heterocyclyl-carbonyl group or a heterocyclyl-C_{1-4} alkyl-carbonyl group, each of which is optionally substituted.

[0124]

The "C_{1-8} alkyl group", "C_{2-8} alkenyl group", "C_{2-8} alkynyl group", "C_{1-8} alkyl-carbonyl group", "C_{3-8} cycloalkyl group", "C_{6-18} aryl group", "C_{6-18} aryl-C_{1-4} alkyl group", "C_{6-18} aryl-carbonyl group", "C_{6-18} aryl-C_{1-4} alkyl-carbonyl group", "heterocyclic group", "heterocyclyl-C_{1-4} alkyl group", "heterocyclyl-carbonyl group" and "heterocyclyl-C_{1-4} alkyl-carbonyl group" are, for example, optionally substituted by one or more (preferably 1 to 5, more preferably 1 to 3) substituent(s) selected from the group consisting of

(a) halogen,

(b) oxo,

(c) optionally halogenated C_{1-4} alkyl,

(d) $-(CH_2)_m-Q$,

(e) $-(CH_2)_m-Z^1-$(optionally halogenated C_{1-4} alkyl),

(f) $-(CH_2)_m-Z^1-C_{3-8}$ cycloalkyl,

(g) $-(CH_2)_m-Z^2-(CH_2)_n-Q$,

(h) $-(CH_2)_m-Z^2-(CH_2)_n-Z^1-$(optionally halogenated C_{1-4} alkyl),

(i) $-(CH_2)_m-Z^2-(CH_2)_n-Z^1-C_{3-8}$ cycloalkyl,

(j) $-(CH_2)_m-Z^1-$(optionally substituted heterocyclic group) (preferably, said heterocyclic group is a 5- to 8-membered heterocyclic group having 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and an optionally oxidized sulfur atom)

(k) $-(CH_2)_m-Z^2-C_{1-4}$ alkoxy, and

(l) $-(CH_2)_m-Z^2-(CH_2)_n-Z^1-(CH_2)_n-Z^1-C_{1-4}$ alkyl (hereinafter to be sometimes to be referred to as substituent group T).

[0125]

In these formulas,

m is an integer of 0 to 4,

n is an integer of 1 to 4,

Q is hydroxy, carboxy, cyano, nitro, $-NR^6R^7$, $-CONR^6R^7$ or $-SO_2NR^6R^7$,

Z^1 is -O-, -CO-, $-C(OH)R^8-$, $-C(=N-OR^8)-$, -S-, -SO-, $-SO_2-$, $-N(COR^8)-$, $-N(CO_2R^9)-$, $-N(SO_2R^9)-$, -CO-O-, -O-CO-, $-CO-NR^8-$, $-NR^8-CO-$, $-NR^8-CO_2-$, $-NR^8-CO-NH-$, $-NR^8-SO_2-$, or $-NR^8-C(=NH)-NH-$, and

Z^2 is -O-, -CO-, $-C(OH)R^8-$, $-C(=N-OR^8)-$, -S-, -SO-, $-SO_2-$, $-NR^8-$, $-N(COR^8)-$, $-N(CO_2R^9)-$, $-N(SO_2R^9)-$, -CO-O-, -O-CO-, $-CO-NR^8-$, $-NR^8-CO-$, $-NR^8-CO_2-$, $-NR^8-CO-NH-$, $-NR^8-C(=NH)-NH-$, $-NR^8-SO_2-$, or $-SO_2-NR^8-$. In these formulas, $(CH_2)_m$ and $(CH_2)_n$ are optionally substituted by one or more (preferably 1 to 5, more preferably 1 to 3) substituents selected from, for example, halogen, optionally halogenated C_{1-4} alkyl and hydroxy, and when m or n is not less than 2, a subset $-CH_2CH_2-$ of $(CH_2)_m$ and $(CH_2)_n$ is optionally replaced by -CH=CH- or -C≡C-.

[0126]

In these formulas, R^6 and R^7 are the same or different and each is a hydrogen atom or C_{1-4} alkyl, or R^6 and R^7 form a ring together with a nitrogen atom. In these formulas, moreover, R^8 is a hydrogen atom or C_{1-4} alkyl and R^9 is C_{1-4}

alkyl. When R^6 and R^7 form a ring together with a nitrogen atom, as the nitrogen-containing heterocyclic group, for example, a 3- to 8-membered (preferably 5- or 6-membered) saturated or unsaturated (preferably saturated) aliphatic heterocyclic group such as azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, heptamethyleneimino, morpholinyl, thiomorpholinyl, piperazinyl, homopiperazinyl and the like, and the like can be mentioned.

[0127]

As X^2, a single bond is preferable.

[0128]

As R^4, a hydrogen atom or a C_{1-8} alkyl group, a C_{2-8} alkenyl group, a C_{6-18} aryl group or heterocyclic group, each of which is optionally substituted is preferable. As the "C_{6-18} aryl group" for R^4, phenyl is preferable. As the "heterocyclic group" for R^4, the aforementioned "5- or 6-membered monocyclic aromatic heterocyclic group" is preferable, and furyl is more preferable.

[0129]

As the "optionally substituted group bonded via a carbon atom or a sulfur atom" for R^2, a C_{1-8} alkyl group, a C_{2-8} alkenyl group, a C_{2-8} alkynyl group, a carbamoyl group, a C_{1-8} alkyl-carbonyl group, a C_{1-8} alkyl-sulfonyl group, a C_{3-8} cycloalkyl group, a C_{6-18} aryl group, a C_{6-18} aryl-C_{1-4} alkyl group, a C_{6-18} aryl-carbonyl group, a C_{6-18} aryl-C_{1-4} alkyl-carbonyl group, a C_{6-18} aryl-sulfonyl group, a heterocyclic group, a heterocyclyl-C_{1-4} alkyl group, a heterocyclyl-carbonyl group or a heterocyclyl-C_{1-4} alkyl-carbonyl group, each of which is optionally substituted, can be mentioned.

[0130]

The "C_{1-8} alkyl group", "C_{2-8} alkenyl group", "C_{2-8} alkynyl group", "C_{1-8} alkyl-carbonyl group", "C_{1-8} alkyl-sulfonyl group", "C_{3-8} cycloalkyl group", "C_{6-18} aryl group", "C_{6-18} aryl-C_{1-4} alkyl group", "C_{6-18} aryl-carbonyl group", "C_{6-18} aryl-C_{1-4} alkyl-carbonyl group", "C_{6-18} aryl-sulfonyl group", "heterocyclic

group", "heterocyclyl-C_{1-4} alkyl group", "heterocyclyl-carbonyl group" and "heterocyclyl-C_{1-4} alkyl-carbonyl group" are optionally substituted by, for example, one or more (preferably 1 to 5, more preferably 1 to 3) substituents selected from the above-mentioned substituent group T.

[0131]

As R^2, a hydrogen atom or a C_{1-8} alkyl group, a C_{6-18} aryl group, a C_{6-18} aryl-C_{1-4} alkyl group, a C_{6-18} aryl-carbonyl group, a C_{6-18} aryl-sulfonyl group or heterocyclyl-C_{1-4} alkyl group, each of which is optionally substituted, is preferable.

[0132]

As the "C_{6-18} aryl group" for R^2, phenyl is preferable. As the "C_{6-18} aryl-C_{1-4} alkyl group" for R^2, benzyl is preferable. As the "C_{6-18} aryl-carbonyl group" for R^2, benzoyl is preferable. As the "C_{6-18} aryl-sulfonyl group" for R^2, phenylsulfonyl is preferable. As the "heterocyclic group" or "heterocyclyl-" of "heterocyclyl-C_{1-4} alkyl group", "heterocyclyl-carbonyl group" and "heterocyclyl-C_{1-4} alkyl-carbonyl group" for R^2, the aforementioned "5- or 6-membered monocyclic aromatic heterocyclic group" or the aforementioned "aliphatic heterocyclic group" is preferable, and furyl or tetrahydrofuryl is more preferable.

[0133]

In the substituents that a group represented by R^2 may have, when R^6 and R^7 form a ring together with a nitrogen atom, the "ring" optionally further has 1 to 5 (preferably 1 to 3) the same or different substituents. As such substituents, substituents similar to those exemplified for "aryl group" or "heterocyclic group" for B can be mentioned.

[0134]

The aforementioned "carbamoyl group" and "ureido group" optionally have 1 or 2 optionally substituted C_{1-8} alkyl group (s). Alternatively, the "carbamoyl group" and "ureido group" may have two substituents and they may form an optionally substituted ring, together with the adjacent nitrogen atom. As

the "ring" of the "optionally substituted ring", rings similar to those formed by R^6 and R^7 together with a nitrogen atom as exemplified above can be mentioned. As the "substituent" of the "optionally substituted C_{1-8} alkyl group" and as the "substituent" of the "optionally substituted ring", groups similar to the substituents of the above-mentioned substituent group T can be mentioned.

[0135]

As the "optionally substituted carbamoyl group", carbamoyl, C_{1-8} alkylcarbamoyl, di(C_{1-8} alkyl)carbamoyl, C_{6-18} aryl-C_{1-4} alkylcarbamoyl, azetidin-1-ylcarbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, piperazin-1-ylcarbonyl, morpholin-4-ylcarbonyl, thiomorpholin-4-ylcarbonyl, (C_{1-4} alkyl)piperidin-1-ylcarbonyl, (C_{6-18} aryl-C_{1-4} alkyl)piperidin-1-ylcarbonyl and the like can be mentioned.

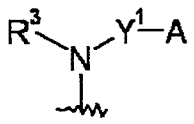
[0136]

As the "optionally substituted ureido group", ureido, 3-(C_{1-8} alkyl)ureido, 3,3-di(C_{1-8} alkyl)ureido, 3-(C_{6-18} aryl-C_{1-4} alkyl)ureido, azetidin-1-ylcarbonylamino, pyrrolidin-1-ylcarbonylamino, piperidin-1-ylcarbonylamino, piperazin-1-ylcarbonylamino, morpholin-4-ylcarbonylamino, thiomorpholin-4-ylcarbonylamino, (C_{1-4} alkyl)piperidin-1-ylcarbonylamino, (C_{6-18} aryl-C_{1-4} alkyl)piperidin-1-ylcarbonylamino and the like can be mentioned.

[0137]

As the "ring structure" of the optionally substituted ring structure formed by R^3 bonded to a carbon atom or a hetero atom on the aryl group or the heteroaryl group represented by A, a saturated or unsaturated (preferably saturated) 4- to 8-membered (preferably 5- or 6-membered) nitrogen-containing heterocycle can be mentioned. Specifically,

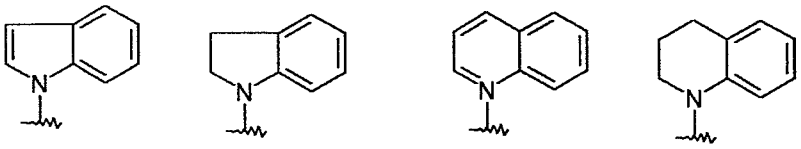
[0138]



[0139]

is

[0140]



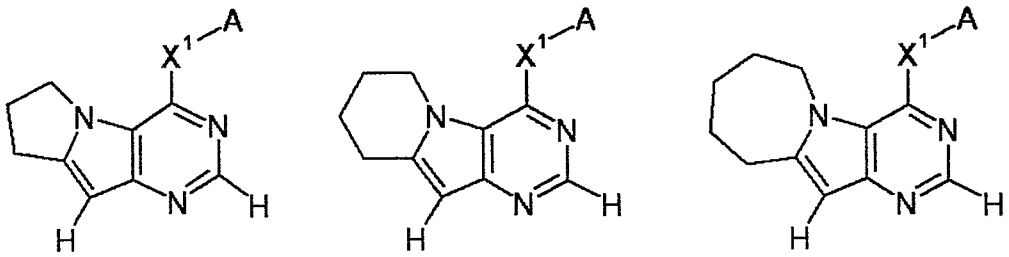
[0141]

The "ring structure" may have 1 to 5 (preferably 1 to 3, more preferably 1 or 2), the same or different substituents at any substitutable position(s). As such substituents, substituents similar to those exemplified for "aryl group" or "heterocyclic group" for B can be mentioned.

[0142]

As the "ring structure" of the optionally substituted ring structure formed by R^1 and R^2 bonded to each other, a saturated or unsaturated (preferably saturated) 4- to 8-membered (preferably 5- or 6-membered) heterocycle can be mentioned. When R^1 and R^2 are bonded to form an optionally substituted ring structure, for example,

[0143]



[0144]

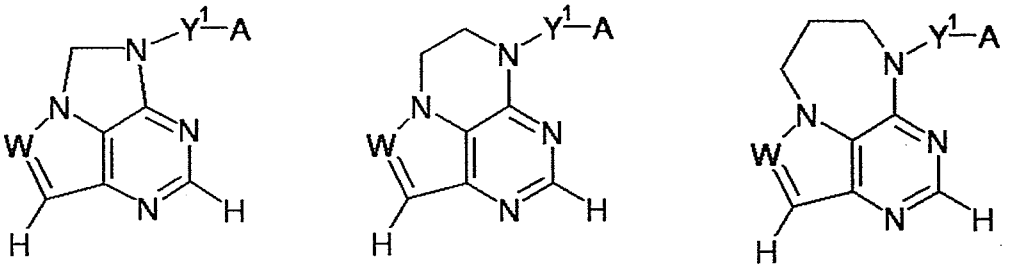
wherein each symbol is as defined above, and the like can be mentioned.

[0145]

As the "ring structure" of the optionally substituted ring structure formed by R^2 and R^3 bonded to each other, a saturated or unsaturated (preferably saturated) 4- to 8-membered (preferably 5- to 7-membered) heterocycle can be mentioned. When R^2 and R^3 are bonded to form an optionally

substituted ring structure, for example,

[0146]



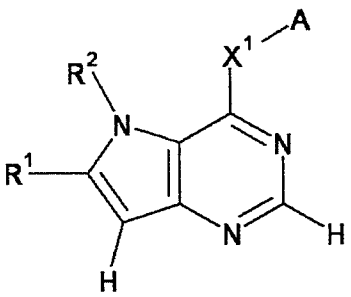
[0147]

wherein each symbol is as defined above, and the like can be mentioned. The "ring structure" formed by R^1 and R^2, or R^2 and R^3 bonded to each other may have 1 to 5 (preferably 1 to 3, more preferably 1 or 2), the same or different substituents selected from the above-mentioned substituent group T at any substitutable position(s).

[0148]

When W is $C(R^1)$, compound (I) is represented by the following formula (IA):

[0149]



(IA)

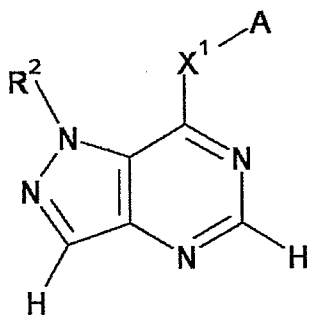
[0150]

wherein each symbol is as defined above.

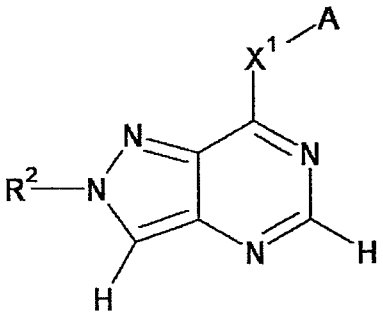
[0151]

When W is N, compound (I) is represented by the following formula (IB) or (IC):

[0152]



(IB)



(IC)

[0153]

wherein each symbol is as defined above.

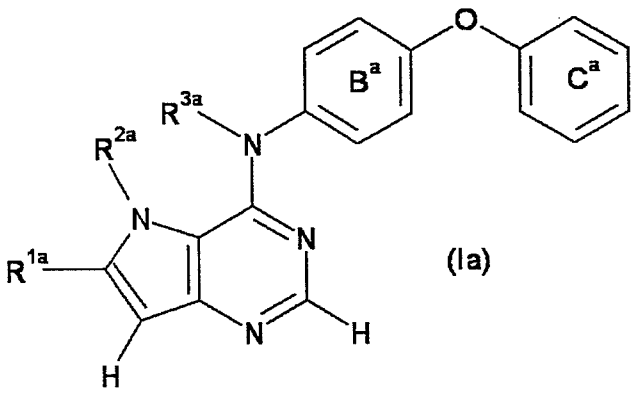
[0154]

Specifically, as compound (I), the following compound (Ia) is specifically preferably used.

[Compound (Ia)]

A compound represented by the formula:

[0155]



(Ia)

[0156]

wherein R^{1a} is a hydrogen atom or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

R^{2a} is an optionally substituted group bonded via a carbon atom or a sulfur atom, or

R^{1a} and R^{2a}, or R^{2a} and R^{3a} are optionally bonded to form an optionally substituted ring structure,

R^{3a} is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or

R^{3a} is optionally bonded to a carbon atom of the adjacent

phenyl group to form an optionally substituted ring structure,
B^a is an optionally substituted benzene ring, and
C^a is an optionally substituted C_{6-18} aryl group,
or a salt thereof.

[0157]

As the "optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom" for R^{1a}, those similar to the "optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom" for R^1 can be used.

[0158]

As the "optionally substituted group bonded via a carbon atom or a sulfur atom" for R^{2a}, those similar to the "optionally substituted group bonded via a carbon atom or a sulfur atom" for R^2 can be used.

[0159]

As the "optionally substituted ring structure" formed by R^{1a} and R^{2a}, or R^{2a} and R^{3a} bonded to each other, those similar to the "optionally substituted ring structure" formed by R^1 and R^2, or R^2 and R^3 bonded to each other can be used.

[0160]

As the "an optionally substituted aliphatic hydrocarbon group" for R^{3a}, those similar to the "optionally substituted aliphatic hydrocarbon group" for R^3 can be used.

[0161]

As the "optionally substituted ring structure" formed by R^{3a} bonded to a carbon atom of the adjacent phenyl group, "optionally substituted ring structure" formed by R^3 bonded to a carbon atom of the adjacent phenyl group can be used.

[0162]

As the substituent of the "optionally substituted benzene ring" for B^a, for example, 1 to 5, the same or different substituents selected from halogen, optionally halogenated C_{1-4} alkyl, hydroxy, optionally halogenated C_{1-4} alkyloxy, C_{1-4} alkyloxymethyl, hydroxyl-C_{1-4} alkyl, C_{1-4} alkyl-carbonyl, carboxy, C_{1-4} alkoxy-carbonyl, cyano, carbamoyl, sulfamoyl, nitro, amino,

C_{1-4} alkyl-carbonylamino, C_{1-4} alkoxy-carbonylamino and C_{1-4} alkyl-sulfonylamino are used.

[0163]

As the "C_{6-18} aryl group" of the "optionally substituted C_{6-18} aryl group" for C^a, for example, phenyl, biphenylyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl and the like are used. Of these, a phenyl group is preferable.

[0164]

As the "substituent" of the "optionally substituted C_{6-18} aryl group" for C^a, those similar to the "optionally substituted benzene ring" for B^a can be used.

[0165]

As R^{2a}, a C_{1-8} alkyl group, a C_{2-8} alkenyl group, a C_{2-8} alkynyl group, a carbamoyl group, a C_{1-8} alkyl-carbonyl group, a C_{1-8} alkyl-sulfonyl group, a C_{3-8} cycloalkyl group, a C_{6-18} aryl group, a C_{6-18} aryl-C_{1-4} alkyl group, a C_{6-18} aryl-carbonyl group, a C_{6-18} aryl-C_{1-4} alkyl-carbonyl group, a C_{6-18} aryl-sulfonyl group, a heterocyclic group, a heterocyclyl-C_{1-4} alkyl group, a heterocyclyl-carbonyl group or a heterocyclyl-C_{1-4} alkyl-carbonyl group, each optionally substituted by 1 to 5 substituents selected from the group consisting of

(a) halogen,

(b) oxo,

(c) optionally halogenated C_{1-4} alkyl,

(d) $-(CH_2)_m-Q$,

(e) $-(CH_2)_m-Z^1-$(optionally halogenated C_{1-4} alkyl),

(f) $-(CH_2)_m-Z^1-C_{3-8}$ cycloalkyl,

(g) $-(CH_2)_m-Z^2-(CH_2)_n-Q$,

(h) $-(CH_2)_m-Z^2-(CH_2)_n-Z^1-$(optionally halogenated C_{1-4} alkyl),

(i) $-(CH_2)_m-Z^2-(CH_2)_n-Z^1-C_{3-8}$ cycloalkyl,

(j) $-(CH_2)_m-Z^1-$(optionally substituted heterocyclic group) (preferably, 5- to 8-membered heterocyclic group having 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and an optionally oxidized sulfur atom),

(k) $-(CH_2)_m-Z^2-C_{1-4}$ alkoxy, and

(l) $-(CH_2)_m-Z^2-(CH_2)_n-Z^1-(CH_2)_n-Z^1-C_{1-4}$ alkyl

wherein m is an integer of 0 to 4,

n is an integer of 1 to 4,

Q is hydroxy, carboxy, cyano, nitro, $-NR^6R^7$, $-CONR^6R^7$, $-OCONH_2$ or $-SO_2NR^6R^7$,

Z^1 is $-O-$, $-CO-$, $-C(OH)R^8-$, $-C(=N-OR^8)-$, $-S-$, $-SO-$, $-SO_2-$, $-N(COR^8)-$, $-N(CO_2R^9)-$, $-N(SO_2R^9)-$, $-CO-O-$, $-O-CO-$, $-CO-NR^8-$, $-NR^8-CO-$, $-NR^8-CO_2-$, $-NR^8-CO-NH-$, $-NR^8-SO_2-$ or $-NR^8-C(=NH)-NH-$,

Z^2 is $-O-$, $-CO-$, $-C(OH)R^8-$, $-C(=N-OR^8)-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^8-$, $-N(COR^8)-$, $-N(CO_2R^9)-$, $-N(SO_2R^9)-$, $-CO-O-$, $-O-CO-$, $-CO-NR^8-$, $-NR^8-CO-$, $-NR^8-CO_2-$, $-NR^8-CO-NH-$, $-NR^8-C(=NH)-NH-$, $-NR^8-SO_2-$ or $-SO_2-NR^8-$,

$(CH_2)_m$ and $(CH_2)_n$ is optionally substituted by 1 to 5 substituents selected from halogen, optionally halogenated C_{1-4} alkyl and hydroxy, when m or n is not less than 2, a subset $-CH_2CH_2-$ of $(CH_2)_m$ and $(CH_2)_n$ may be replaced by $-CH=CH-$ or $-C\equiv C-$,

R^6 and R^7 are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group, or R^6 and R^7 are bond to form, together with a nitrogen atom, a 3- to 8-membered saturated or unsaturated aliphatic heterocyclic group,

R^8 is a hydrogen atom or C_{1-4} alkyl and

R^9 is C_{1-4} alkyl,

is preferable.

[0166]

As compound (Ia), a compound wherein

B^a is a benzene ring optionally substituted by 1 to 4 substituents selected from halogen, C_{1-4} alkyl, hydroxy-C_{1-4} alkyl and C_{1-4} alkyloxy;

C^a is a phenyl group optionally substituted by 1 to 5 substituents selected from (i) halogen, (ii) optionally halogenated C_{1-4} alkyl, (iii) hydroxy-C_{1-4} alkyl, (iv) heterocyclyl-C_{1-4} alkyl (preferably, 5- to 8-membered heterocyclyl-C_{1-4} alkyl, said 5- to 8-membered heterocycle has 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen

atom and an optionally oxidized sulfur atom, and includes imidazolyl, triazolyl and the like), (v) optionally halogenated C_{1-4} alkyloxy, (vi) C_{1-4} alkyl-carbonyl, (vii) cyano, (viii) carbamoyl optionally substituted by C_{1-8} alkyl and (ix) C_{1-4} alkoxy-carbonyl;

R^{1a} is

(i) a hydrogen atom,

(ii) a cyano group, or

(iii) a C_{1-4} alkyl group or a C_{2-4} alkenyl group, each of which is optionally substituted by $-NR^8-CO-(CH_2)_n-NR^6R^7$

wherein n is an integer of 1 to 4, R^6 and R^7 are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group, R^8 is a hydrogen atom or a C_{1-4} alkyl group, and when n is not less than 2, a subset $-CH_2CH_2-$ of $(CH_2)_n$ is optionally replaced by $-CH=CH-$;

R^{2a} is a C_{1-8} alkyl group, a C_{2-8} alkenyl group or a C_{2-8} alkynyl group, each of which is optionally substituted by substituent(s) selected from

(a) hydroxy,

(b) carboxy,

(c) cyano,

(d) optionally halogenated C_{1-4} alkyloxy,

(e) $-O-(CH_2)_n-OH$,

(f) $-O-(CH_2)_n-O-CO-NH_2$,

(g) $-O-(CH_2)_n-O-$(optionally halogenated C_{1-4} alkyl),

(h) $-O-(CH_2)_n-SO_2-$(optionally halogenated C_{1-4} alkyl),

(i) $-O-(CH_2)_n-SO_2-C_{6-18}$ aryl,

(j) $-O-(CH_2)_n-SO_2-(CH_2)_n-OH$,

(k) $-O-(CH_2)_n-NR^8-CO-C_{1-4}$ alkyl,

(l) $-O-(CH_2)_n-NR^8-CO-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(m) $-O-(CH_2)_n-NR^8-SO_2-$(optionally halogenated C_{1-4} alkyl),

(n) $-CO-NR^8-(CH_2)_n-OH$,

(o) $-CO-NR^8-(CH_2)_n-SO_2-$(optionally halogenated C_{1-4} alkyl),

(p) $-CO-NR^8-O-C_{1-4}$ alkyl,

(q) $-NR^6R^7$,

(r) $-NR^8-(CH_2)_n-OH$,

(s) $-NR^8-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(t) $-NR^8-CO-$(optionally halogenated C_{1-4} alkyl),

(u) $-NR^8-CO-(CH_2)_n-OH$,

(v) $-NR^8-CO-(CH_2)_n-CN$,

(w) $-NR^8-CO-(CH_2)_n-NR^6R^7$,

(x) $-NR^8-CO-(CH_2)_n-O-C_{1-4}$ alkyl,

(y) $-NR^8-CO-(CH_2)_n-SO-$(optionally halogenated C_{1-4} alkyl),

(z) $-NR^8-CO-(CH_2)_n-SO_2-$(optionally halogenated C_{1-4} alkyl),

(aa) $-NR^8-CO-(CH_2)_n-SO_2-C_{3-8}$ cycloalkyl,

(bb) $-NR^8-CO-(CH_2)_n-NR^8-SO_2-C_{1-4}$ alkyl,

(cc) $-NR^8-CO_2-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(dd) $-NR^8-CO-NH-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(ee) $-NR^8-CO-NH-O-C_{1-4}$ alkyl,

(ff) $-NR^8-CO-NH-(CH_2)_n-O-C_{1-4}$ alkyl,

(gg) $-NR^8-C(=NH)-NH-C_{1-4}$ alkyl,

(hh) $-NR^8-SO_2-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(ii) $-S-(CH_2)_n-OH$,

(jj) $-SO-(CH_2)_n-OH$,

(kk) $-SO_2-(CH_2)_n-OH$, and

(ll) $-NR^8-CO-$(optionally substituted heterocyclic group)

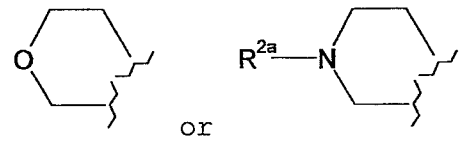
(preferably, said heterocyclic group is a 5- to 8-membered heterocyclic group having 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and an optionally oxidized sulfur atom, which is optionally substituted by substituent(s) selected from hydroxy, C_{1-4} alkyl, optionally oxidized C_{1-4} alkylthio, $-CO-C_{1-4}$ alkyl, $-CO-O-C_{1-4}$ alkyl, $-CO-NH-C_{1-4}$ alkyl, $-CONH_2$, $-SO_2-C_{1-4}$ alkyl, $-SO_2-NH-C_{1-4}$ alkyl, $-SO_2NH_2$ and the like),

wherein n is an integer of 1 to 4, R^6 and R^7 are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group, R^8 is a hydrogen atom or a C_{1-4} alkyl group, $(CH_2)_n$ is optionally substituted by optionally halogenated C_{1-4} alkyl or hydroxy, and when n is not less than 2, a subset $-CH_2CH_2-$ of $(CH_2)_n$ is optionally replaced by $-CH=CH-$; and

R^{3a} is a hydrogen atom or a C_{1-6} alkyl group; or

R^{1a} and R^{2a} are optionally bonded to form

[0167]



or

[0168]

R^{2a} and R^{3a} are optionally bonded to form C_{2-4} alkylene optionally substituted by an imino group, is preferable.

As R^8, a hydrogen atom, methyl, ethyl and the like are preferable, and a hydrogen atom is particularly preferable.

Among those, as R^{2a}, a C_{1-8} alkyl group, a C_{2-8} alkenyl group or a C_{2-8} alkynyl group, each of which is optionally substituted by substituent(s) selected from

(a) hydroxy,

(b) carboxy,

(c) cyano,

(d) optionally halogenated C_{1-4} alkyloxy,

(e) $-O-(CH_2)_n-OH$ (wherein $(CH_2)_n$ is optionally substituted by hydroxy),

(f) $-O-(CH_2)_n-O-CO-NH_2$,

(g) $-O-(CH_2)_n-O-$(optionally halogenated C_{1-4} alkyl),

(h) $-O-(CH_2)_n-SO_2-$(optionally halogenated C_{1-4} alkyl),

(i) $-O-(CH_2)_n-SO_2-C_{6-18}$ aryl,

(j) $-O-(CH_2)_n-SO_2-(CH_2)_n-OH$,

(k) $-O-(CH_2)_n-NR^8-CO-C_{1-4}$ alkyl,

(l) $-O-(CH_2)_n-NR^8-CO-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(m) $-O-(CH_2)_n-NR^8-SO_2-$(optionally halogenated C_{1-4} alkyl),

(n) $-CO-NR^8-(CH_2)_n-OH$,

(o) $-CO-NR^8-(CH_2)_n-SO_2-$(optionally halogenated C_{1-4} alkyl),

(p) $-CO-NR^8-O-C_{1-4}$ alkyl,

(q) $-NR^6R^7$,

(r) $-NR^8-(CH_2)_n-OH$,

(s) $-NR^8-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(t) $-NR^8-CO-$(optionally halogenated C_{1-4} alkyl),

(u) $-NR^8-CO-(CH_2)_n-OH$ (wherein $(CH_2)_n$ is optionally substituted by optionally halogenated C_{1-4} alkyl or hydroxy),

(v) $-NR^8-CO-(CH_2)_n-CN$,

(w) $-NR^8-CO-(CH_2)_n-NR^6R^7$ (when n is not less than 2, a subset $-CH_2CH_2-$ of $(CH_2)_n$ is optionally replaced by $-CH=CH-$),

(x) $-NR^8-CO-(CH_2)_n-O-C_{1-4}$ alkyl,

(y) $-NR^8-CO-(CH_2)_n-SO-$(optionally halogenated C_{1-4} alkyl),

(z) $-NR^8-CO-(CH_2)_n-SO_2-$(optionally halogenated C_{1-4} alkyl) (wherein $(CH_2)_n$ is optionally substituted by C_{1-4} alkyl),

(aa) $-NR^8-CO-(CH_2)_n-SO_2-C_{3-8}$ cycloalkyl,

(bb) $-NR^8-CO-(CH_2)_n-NR^8-SO_2-C_{1-4}$ alkyl,

(cc) $-NR^8-CO_2-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(dd) $-NR^8-CO-NH-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(ee) $-NR^8-CO-NH-O-C_{1-4}$ alkyl,

(ff) $-NR^8-CO-NH-(CH_2)_n-O-C_{1-4}$ alkyl,

(gg) $-NR^8-C(=NH)-NH-C_{1-4}$ alkyl,

(hh) $-NR^8-SO_2-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(ii) $-S-(CH_2)_n-OH$,

(jj) $-SO-(CH_2)_n-OH$,

(kk) $-SO_2-(CH_2)_n-OH$, and

(ll) $-NR^8-CO-$(optionally substituted heterocyclic group) (preferably, said heterocyclic group is a 5- to 8-membered heterocyclic group having 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and an optionally oxidized sulfur atom, which is optionally substituted by substituent(s) selected from hydroxy, C_{1-4} alkyl, optionally oxidized C_{1-4} alkylthio, $-CO-C_{1-4}$ alkyl, $-CO-O-C_{1-4}$ alkyl, $-CO-NH-C_{1-4}$ alkyl, $-CONH_2$, $-SO_2-C_{1-4}$ alkyl, $-SO_2-NH-C_{1-4}$ alkyl, $-SO_2NH_2$ and the like),

wherein n is an integer of 1 to 4, R^6 and R^7 are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group, and R^8 is a hydrogen atom or a C_{1-4} alkyl group, is preferable.

As R^8, a hydrogen atom, methyl, ethyl and the like are

preferable, and a hydrogen atom is particularly preferable.

[0169]

As compound (Ia), moreover, a compound wherein

B^a is a benzene ring optionally substituted by 1 to 4 substituents selected from halogen and optionally halogenated C_{1-4} alkyl;

C^a is a phenyl group substituted by 1 to 5 substituents selected from (i) halogen, (ii) optionally halogenated C_{1-4} alkyl, (iii) hydroxy-C_{1-4} alkyl, (iv) heterocyclyl-C_{1-4} alkyl (preferably, 5- to 8-membered heterocyclyl-C_{1-4} alkyl, said 5- to 8-membered heterocycle has 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and an optionally oxidized sulfur atom, and includes imidazolyl and the like), (v) optionally halogenated C_{1-4} alkyloxy, (vi) cyano, and (vii) carbamoyl optionally substituted by C_{1-8} alkyl;

R^{1a} is a hydrogen atom;

R^{2a} is a C_{1-8} alkyl group, a C_{2-8} alkenyl group or a C_{2-8} alkynyl group, each of which is substituted by substituent(s) selected from

(a) hydroxy,

(b) optionally halogenated C_{1-4} alkyloxy,

(c) $-O-(CH_2)_n-OH$,

(d) $-O-(CH_2)_n-O-CO-NH_2$,

(e) $-O-(CH_2)_n-O-C_{1-4}$ alkyl,

(f) $-O-(CH_2)_n-SO_2-$(optionally halogenated C_{1-4} alkyl),

(g) $-O-(CH_2)_n-SO_2-C_{6-18}$ aryl,

(h) $-O-(CH_2)_n-SO_2-(CH_2)_n-OH$,

(i) $-O-(CH_2)_n-NR^8-SO_2-$(optionally halogenated C_{1-4} alkyl),

(j) $-CO-NR^8-(CH_2)_n-OH$,

(k) $-CO-NR^8-(CH_2)_n-SO_2-$(optionally halogenated C_{1-4} alkyl),

(l) $-NR^6R^7$,

(m) $-NR^8-(CH_2)_n-OH$,

(n) $-NR^8-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(o) $-NR^8-CO-(CH_2)_n-OH$,

(p) $-NR^8-CO-(CH_2)_n-O-C_{1-4}$ alkyl,

(q) $-NR^8-CO-(CH_2)_n-SO-$(optionally halogenated C_{1-4} alkyl),

(r) $-NR^8-CO-(CH_2)_n-SO_2-$(optionally halogenated C_{1-4} alkyl),

(s) $-NR^8-CO-(CH_2)_n-SO_2-C_{3-8}$ cycloalkyl,

(t) $-NR^8-CO_2-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(u) $-NR^8-CO-NH-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(v) $-NR^8-SO_2-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(w) $-S-(CH_2)_n-OH$,

(x) $-SO-(CH_2)_n-OH$,

(y) $-SO_2-(CH_2)_n-OH$, and

(z) $-NR^8-CO-$(optionally substituted heterocyclic group)

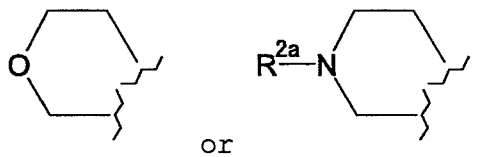
(preferably, said heterocyclic group is a 5- to 8-membered heterocyclic group having 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and an optionally oxidized sulfur atom, which is optionally substituted by substituent(s) selected from hydroxy, C_{1-4} alkyl, optionally oxidized C_{1-4} alkylthio, $-CO-C_{1-4}$ alkyl, $-CO-NH-C_{1-4}$ alkyl, $-CONH_2$, $-SO_2-C_{1-4}$ alkyl, $-SO_2-NH-C_{1-4}$ alkyl, $-SO_2NH_2$ and the like),

wherein n is an integer of 1 to 4, R^6 and R^7 are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group, R^8 is a hydrogen atom or a C_{1-4} alkyl group, and $(CH_2)_n$ is optionally substituted by C_{1-4} alkyl or hydroxy;

R^{3a} is a hydrogen atom or a C_{1-6} alkyl group; or

R^{1a} and R^{2a} are optionally bonded to form

[0170]



or ; or

[0171]

R^{2a} and R^{3a} are optionally bonded to form C_{2-4} alkylene, is preferable.

[0172]

Of these, as R^{2a}, a C_{1-8} alkyl group, a C_{2-8} alkenyl group or a C_{2-8} alkynyl group (particularly, a C_{1-8} alkyl group), each of which is substituted by substituent(s) selected from

(a) hydroxy,

(b) optionally halogenated C_{1-4} alkyloxy,

(c) $-O-(CH_2)_n-OH$ (wherein $(CH_2)_n$ is optionally substituted by hydroxy),

(d) $-O-(CH_2)_n-O-CO-NH_2$,

(e) $-O-(CH_2)_n-O-C_{1-4}$ alkyl,

(f) $-O-(CH_2)_n-SO_2-$(optionally halogenated C_{1-4} alkyl),

(g) $-O-(CH_2)_n-SO_2-C_{6-18}$ aryl,

(h) $-O-(CH_2)_n-SO_2-(CH_2)_n-OH$,

(i) $-O-(CH_2)_n-NR^8-SO_2-$(optionally halogenated C_{1-4} alkyl),

(j) $-CO-NR^8-(CH_2)_n-OH$,

(k) $-CO-NR^8-(CH_2)_n-SO_2-$(optionally halogenated C_{1-4} alkyl),

(l) $-NR^6R^7$,

(m) $-NR^8-(CH_2)_n-OH$,

(n) $-NR^8-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(o) $-NR^8-CO-(CH_2)_n-OH$ (wherein $(CH_2)_n$ is optionally substituted by C_{1-4} alkyl),

(p) $-NR^8-CO-(CH_2)_n-O-C_{1-4}$ alkyl,

(q) $-NR^8-CO-(CH_2)_n-SO-$(optionally halogenated C_{1-4} alkyl),

(r) $-NR^8-CO-(CH_2)_n-SO_2-$(optionally halogenated C_{1-4} alkyl) (wherein $(CH_2)_n$ is optionally substituted by C_{1-4} alkyl),

(s) $-NR^8-CO-(CH_2)_n-SO_2-C_{3-8}$ cycloalkyl,

(t) $-NR^8-CO_2-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(u) $-NR^8-CO-NH-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(v) $-NR^8-SO_2-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(w) $-S-(CH_2)_n-OH$,

(x) $-SO-(CH_2)_n-OH$,

(y) $-SO_2-(CH_2)_n-OH$, and

(z) $-NR^8-CO-$(optionally substituted heterocyclic group) (preferably, said heterocyclic group is a 5- to 8-membered heterocyclic group having 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and an optionally oxidized sulfur atom, which is optionally substituted by substituent(s) selected from hydroxy, C_{1-4} alkyl, optionally oxidized C_{1-4} alkylthio, $-CO-C_{1-4}$ alkyl, $-CO-NH-C_{1-4}$ alkyl, $-CONH_2$, $-SO_2-C_{1-4}$

alkyl, $-SO_2-NH-C_{1-4}$ alkyl, $-SO_2NH_2$ and the like),

wherein n is an integer of 1 to 4, R^6 and R^7 are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group, R^8 is a hydrogen atom or a C_{1-4} alkyl group, is preferable.

[0173]

As R^{2a}, (i) a C_{5-8} alkyl group substituted by hydroxy, (ii) a C_{1-8} alkyl group substituted by substituent(s) selected from

(a) halogenated C_{1-4} alkyloxy,

(b) $-O-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-O-CO-NH_2$,

(d) $-O-(CH_2)_n-O-$(optionally halogenated C_{1-4} alkyl),

(e) $-O-(CH_2)_n-SO_2-$(optionally halogenated C_{1-4} alkyl),

(f) $-O-(CH_2)_n-SO_2-C_{6-18}$ aryl,

(g) $-O-(CH_2)_n-NR^8-SO_2-$(optionally halogenated C_{1-4} alkyl),

(h) $-CO-NR^8-(CH_2)_n-OH$,

(i) $-CO-NR^8-(CH_2)_n-SO_2-$(optionally halogenated C_{1-4} alkyl),

(j) $-NR^8-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(k) $-NR^8-CO-(CH_2)_n-OH$,

(l) $-NR^8-CO-(CH_2)_n-O-C_{1-4}$ alkyl,

(m) $-NR^8-CO-(CH_2)_n-SO-$(optionally halogenated C_{1-4} alkyl),

(n) $-NR^8-CO-(CH_2)_n-SO_2-$(optionally halogenated C_{1-4} alkyl),

(o) $-NR^8-CO-(CH_2)_n-SO_2-C_{3-8}$ cycloalkyl,

(p) $-NR^8-CO_2-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(q) $-NR^8-CO-NH-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(r) $-NR^8-SO_2-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(s) $-S-(CH_2)_n-OH$,

(t) $-SO-(CH_2)_n-OH$,

(u) $-SO_2-(CH_2)_n-OH$, and

(v) $-NR^8-CO-$(optionally substituted heterocyclic group)

(preferably, said heterocyclic group is a 5- to 8-membered heterocyclic group having 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and an optionally oxidized sulfur atom, which is optionally substituted by substituent(s) selected from hydroxy, C_{1-4} alkyl, optionally oxidized C_{1-4}

alkylthio, -CO-C_{1-4} alkyl, -CO-NH-C_{1-4} alkyl, -$CONH_2$, -SO_2-C_{1-4} alkyl, -SO_2-NH-C_{1-4} alkyl, -SO_2NH_2 and the like),

wherein n is an integer of 1 to 4, R^8 is a hydrogen atom or a C_{1-4} alkyl group, and $(CH_2)_n$ is optionally substituted by C_{1-4} alkyl or hydroxy,

(iii) a C_{2-8} alkenyl group optionally substituted by hydroxy, or (iv) a C_{2-8} alkynyl group optionally substituted by hydroxy is preferable, and particularly,

as R^{2a}, (i) a C_{5-8} alkyl group substituted by hydroxy,

(ii) a C_{1-8} alkyl group substituted by substituent(s) selected from

(a) halogenated C_{1-4} alkyloxy,

(b) -O-$(CH_2)_n$-OH (wherein $(CH_2)_n$ is optionally substituted by hydroxy),

(c) -O-$(CH_2)_n$-O-CO-NH_2,

(d) -O-$(CH_2)_n$-O-(optionally halogenated C_{1-4} alkyl),

(e) -O-$(CH_2)_n$-SO_2-(optionally halogenated C_{1-4} alkyl),

(f) -O-$(CH_2)_n$-SO_2-C_{6-18} aryl,

(g) -O-$(CH_2)_n$-NR^8-SO_2-(optionally halogenated C_{1-4} alkyl),

(h) -CO-NR^8-$(CH_2)_n$-OH,

(i) -CO-NR^8-$(CH_2)_n$-SO_2-(optionally halogenated C_{1-4} alkyl),

(j) -NR^8-$(CH_2)_n$-SO_2-C_{1-4} alkyl,

(k) -NR^8-CO-$(CH_2)_n$-OH (wherein $(CH_2)_n$ is optionally substituted by C_{1-4} alkyl),

(l) -NR^8-CO-$(CH_2)_n$-O-C_{1-4} alkyl,

(m) -NR^8-CO-$(CH_2)_n$-SO-(optionally halogenated C_{1-4} alkyl),

(n) -NR^8-CO-$(CH_2)_n$-SO_2-(optionally halogenated C_{1-4} alkyl) (wherein $(CH_2)_n$ is optionally substituted by C_{1-4} alkyl),

(o) -NR^8-CO-$(CH_2)_n$-SO_2-C_{3-8} cycloalkyl,

(p) -NR^8-CO_2-$(CH_2)_n$-SO_2-C_{1-4} alkyl,

(q) -NR^8-CO-NH-$(CH_2)_n$-SO_2-C_{1-4} alkyl,

(r) -NR^8-SO_2-$(CH_2)_n$-SO_2-C_{1-4} alkyl,

(s) -S-$(CH_2)_n$-OH,

(t) -SO-$(CH_2)_n$-OH,

(u) -SO_2-$(CH_2)_n$-OH, and

(v) $-NR^8-CO-$(optionally substituted heterocyclic group) (preferably, said heterocyclic group is a 5- to 8-membered heterocyclic group having 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom and an optionally oxidized sulfur atom, which is optionally substituted by substituent(s) selected from hydroxy, C_{1-4} alkyl, optionally oxidized C_{1-4} alkylthio, $-CO-C_{1-4}$ alkyl, $-CO-NH-C_{1-4}$ alkyl, $-CONH_2$, $-SO_2-C_{1-4}$ alkyl, $-SO_2-NH-C_{1-4}$ alkyl, $-SO_2NH_2$ and the like),

wherein n is an integer of 1 to 4, and R^8 is a hydrogen atom or a C_{1-4} alkyl group,

(iii) a C_{2-8} alkenyl group optionally substituted by hydroxy, or (iv) a C_{2-8} alkynyl group optionally substituted by hydroxy, is preferable.

[0174]

As R^8, a hydrogen atom, methyl, ethyl and the like are preferable, and a hydrogen atom is particularly preferable.

[0175]

Compound (I) is preferably a compound wherein A is an aryl group substituted by a group represented by the formula $-Y^2-B$

wherein Y^2 is a single bond, -O-, $-OCH_2-$, -NH- or -S-, and B is an aryl group, a heterocyclic group, a C_{3-8} cycloalkyl group, a carbamoyl group, a ureido group, a C_{6-18} aryl-carbonyl group or a C_{6-18} aryl-C_{1-4} alkyl-carbonyl group, each of which is optionally substituted,

which aryl group is optionally further substituted.

[0176]

A preferable embodiment of compound (I) is a compound wherein W is $C(R^1)$;

A is an aryl group substituted by a group represented by the formula $-Y^2-B$

wherein Y^2 is a single bond, -O-, $-OCH_2-$, -NH- or -S-, and B is an aryl group, a heterocyclic group, a C_{3-8} cycloalkyl group, a carbamoyl group, a ureido group, a C_{6-18} aryl-carbonyl group or a C_{6-18} aryl-C_{1-4} alkyl-carbonyl group, each

of which is optionally substituted,

which aryl group is optionally further substituted;

R^1 is a group represented by the formula $-X^2-R^4$ wherein X^2 is a single bond, -NH- or -O-, and R^4 is a hydrogen atom or a C_{1-8} alkyl group, a C_{2-8} alkenyl group, a C_{2-8} alkynyl group, a carbamoyl group, a C_{1-8} alkyl-carbonyl group, a C_{3-8} cycloalkyl group, a C_{6-18} aryl group, a C_{6-18} aryl-C_{1-4} alkyl group, a C_{6-18} aryl-carbonyl group, a C_{6-18} aryl-C_{1-4} alkyl-carbonyl group, a heterocyclic group, a heterocyclyl-C_{1-4} alkyl group, a heterocyclyl-carbonyl group or a heterocyclyl-C_{1-4} alkyl-carbonyl group, each of which is optionally substituted;

R^2 is a hydrogen atom or a C_{1-8} alkyl group, a C_{2-8} alkenyl group, a C_{2-8} alkynyl group, a carbamoyl group, a C_{1-8} alkyl-carbonyl group, a C_{1-8} alkylsulfonyl group, a C_{3-8} cycloalkyl group, a C_{6-18} aryl group, a C_{6-18} aryl-C_{1-4} alkyl group, a C_{6-18} aryl-carbonyl group, a C_{6-18} aryl-C_{1-4} alkyl-carbonyl group, a C_{6-18} aryl-sulfonyl group, a heterocyclic group, a heterocyclyl-C_{1-4} alkyl group, a heterocyclyl-carbonyl group or a heterocyclyl-C_{1-4} alkyl-carbonyl group, each of which is optionally substituted; and

X^1 is $-NR^3-$ wherein R^3 is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group.

[0177]

Another preferable embodiment of compound (I) is a compound wherein W is N;

X^1 is $-NR^3-$

wherein R^3 is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group; and

A is an aryl group substituted by a group represented by the formula $-Y^2-B$

wherein Y^2 is a single bond, -O-, $-OCH_2-$, -NH- or -S-, and B is an aryl group, a heterocyclic group, a C_{3-8} cycloalkyl group, a carbamoyl group, a ureido group, a C_{6-18} aryl-carbonyl group or a C_{6-18} aryl-C_{1-4} alkyl-carbonyl group, each of which is optionally substituted,

which aryl group is optionally further substituted; and

R^2 is a hydrogen atom or a C_{1-8} alkyl group, a C_{2-8} alkenyl group, a C_{2-8} alkynyl group, a carbamoyl group, a C_{1-8} alkyl-carbonyl group, a C_{1-8} alkylsulfonyl group, a C_{3-8} cycloalkyl group, a C_{6-18} aryl group, a C_{6-18} aryl-C_{1-4} alkyl group, a C_{6-18} aryl-carbonyl group, a C_{6-18} aryl-C_{1-4} alkyl-carbonyl group, a C_{6-18} aryl-sulfonyl group, a heterocyclic group, a heterocyclyl-C_{1-4} alkyl group, a heterocyclyl-carbonyl group or a heterocyclyl-C_{1-4} alkyl-carbonyl group, each of which is optionally substituted.

[0178]

A still another preferable embodiment of compound (I) is a compound wherein W is N;

X^1 is $-NR^3-$;

A is an aryl group substituted by a group represented by the formula $-Y^2-B$

wherein Y^2 is a single bond, -O-, $-OCH_2-$, -NH- or -S-, and B is an aryl group, a heterocyclic group, a C_{3-8} cycloalkyl group, a carbamoyl group, a ureido group, a C_{6-18} aryl-carbonyl group or a C_{6-18} aryl-C_{1-4} alkyl-carbonyl group, each of which is optionally substituted,

which aryl group is optionally further substituted; and

R^2 and R^3 are bonded to form an optionally substituted ring structure.

[0179]

As the salts of the compound represented by the formula (I), for example, metal salt, ammonium salt, salts with organic base, salts with inorganic acid, salts with organic acid, salts with basic or acidic amino acid and the like can be mentioned. As preferable examples of the metal salt, for example, alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt, barium salt and the like; aluminum salt and the like can be mentioned. As preferable examples of the salts with organic base, for example, salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-

lutidine, ethanolamine, diethanolamine, triethanolamine, tromethamine [tris(hydroxymethyl)methylamine], t-butylamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like can be mentioned. As preferable examples of salts with inorganic acid, for example, salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like can be mentioned. As preferable examples of the salts with organic acid, for example, salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like can be mentioned. As preferable examples of the salts with basic amino acid, for example, salts with arginine, lysine, ornithine and the like can be mentioned, and as preferable examples of the salts with acidic amino acid, for example, salts with aspartic acid, glutamic acid and the like can be mentioned.

[0180]

Of these, pharmaceutically acceptable salts are preferable. For example, when a compound contains an acidic functional group, inorganic salts such as alkali metal salts (e.g., sodium salt, potassium salt etc.), alkaline earth metal salts (e.g., calcium salt, magnesium salt, barium salt etc.) and the like, ammonium salt and the like, and when a compound contains a basic functional group, for example, salts with inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like, or salts with organic acid such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid and the like can be mentioned.

[0181]

Each term used for the compound of the formula (I') (hereinafter sometimes to be abbreviated as compound (I')) is

explained in the following.

[0182]

In compound (I'), unless otherwise specified, the "halogen atom" (and "halogen" in substituents) is, for example, a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

[0183]

In compound (I'), unless otherwise specified, the "alkyl group" is, for example, straight chain or branched alkyl group having a carbon number of 1 to 10 (e.g., 1 - 10, 1 - 8, 1 - 6, 2 - 6, 1 - 4), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, heptyl, octyl, nonyl, decyl and the like.

[0184]

In compound (I'), unless otherwise specified, the "C_{1-10} alkyl group is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, heptyl, octyl, nonyl, decyl or the like.

[0185]

In compound (I'), unless otherwise specified, the "C_{1-8} alkyl group" is, for example, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, heptyl, octyl or the like.

[0186]

In compound (I'), unless otherwise specified, the "C_{1-6} alkyl group" is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl or the like.

[0187]

In compound (I'), unless otherwise specified, the "C_{2-6} alkyl group" is, for example, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl or the like.

[0188]

In compound (I'), unless otherwise specified, the "C_{1-4} alkyl group" is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl or the like.

[0189]

In compound (I'), unless otherwise specified, the "alkenyl group" is, for example, an alkenyl group having a carbon number of 2 to 10 (e.g., 2 - 10, 2 - 8, 2 - 6, 2 - 4), such as ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl, 5-hexenyl, 1-heptenyl, 1-octenyl and the like.

[0190]

In compound (I'), unless otherwise specified, the "C_{2-10} alkenyl group" is, for example, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl, 5-hexenyl, 1-heptenyl, 1-octenyl or the like.

[0191]

In compound (I'), unless otherwise specified, the "C_{2-8} alkenyl group" is, for example, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl, 5-hexenyl, 1-heptenyl, 1-octenyl or the like.

[0192]

In compound (I'), unless otherwise specified, the "C_{2-6}

alkenyl group" is, for example, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl, 5-hexenyl or the like.

[0193]

In compound (I'), unless otherwise specified, the "C_{2-4} alkenyl group" is, for example, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl or the like.

[0194]

In compound (I'), unless otherwise specified, the "alkynyl group" is, for example, an alkynyl group having a carbon number of 2 to 10 (e.g., 2 - 10, 2 - 8, 2 - 6, 2 - 4), such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 1-octynyl and the like.

[0195]

In compound (I'), unless otherwise specified, the "C_{2-10} alkynyl group" is, for example, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 1-octynyl or the like.

[0196]

In compound (I'), unless otherwise specified, the "C_{2-8} alkynyl group" is, for example, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 1-octynyl or the like.

[0197]

In compound (I'), unless otherwise specified, the "C_{2-6} alkynyl group" is, for example, ethynyl, 1-propynyl, 2-

propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl or the like.

[0198]

In compound (I'), unless otherwise specified, the "C_{2-4} alkynyl group" is, for example, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl or the like.

[0199]

In compound (I'), unless otherwise specified, the "cycloalkyl group" is, for example, a cycloalkyl group having a carbon number of 3 to 10 (e.g., 3 - 10, 3 - 8, 3 - 7, 3 - 6, 5 - 8), such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, bicyclo[4.3.1]decyl, adamantyl and the like.

[0200]

In compound (I'), unless otherwise specified, the "C_{3-10} cycloalkyl group" is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, bicyclo[4.3.1]decyl, adamantyl or the like.

[0201]

In compound (I'), unless otherwise specified, the "C_{3-8} cycloalkyl group" is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl or the like.

[0202]

In compound (I'), unless otherwise specified, the "C_{3-7} cycloalkyl group" is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like.

[0203]

In compound (I'), unless otherwise specified, the "C_{5-8}

cycloalkyl group" is, for example, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or the like.

[0204]

In compound (I'), unless otherwise specified, the "cycloalkenyl group" is, for example, a cycloalkenyl group having a carbon number of 3 to 10, such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl and the like.

[0205]

In compound (I'), unless otherwise specified, the "C_{3-10} cycloalkenyl group" is, for example, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl or the like.

[0206]

In compound (I'), unless otherwise specified, the "cycloalkadienyl group" is, for example, a cycloalkadienyl group having a carbon number of 4 to 10, such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl and the like.

[0207]

In compound (I'), unless otherwise specified, the "C_{4-10} cycloalkadienyl group" is, for example, 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl or the like.

[0208]

In compound (I'), unless otherwise specified, the "aryl group" includes a monocyclic aryl group and a condensed polycyclic aryl group. The "aryl group" is, for example, an aryl group having a carbon number of 6 to 18 (e.g., 6 - 18, 6 - 14, 6 - 10), such as phenyl, naphthyl, anthryl, phenanthryl, acenaphthyl, biphenylyl and the like.

[0209]

In compound (I'), unless otherwise specified, the "C_{6-18} aryl group" is, for example, phenyl, naphthyl, anthryl, phenanthryl, acenaphthyl, biphenylyl or the like.

[0210]

In compound (I'), unless otherwise specified, the "C_{6-14} aryl group" is, for example, phenyl, naphthyl, anthryl, phenanthryl, acenaphthyl, biphenylyl or the like.

[0211]

In compound (I'), unless otherwise specified, the "C_{6-10} aryl group" is, for example, phenyl, naphthyl or the like.

[0212]

In compound (I'), unless otherwise specified, the "aralkyl group" is, for example, an aralkyl group having a carbon number of 7 to 16, such as benzyl, phenethyl, phenylpropyl, naphthylmethyl, biphenylylmethyl and the like.

[0213]

In compound (I'), unless otherwise specified, the "C_{7-16} aralkyl group" is, for example, benzyl, phenethyl, phenylpropyl, naphthylmethyl, biphenylylmethyl or the like.

[0214]

In compound (I'), unless otherwise specified, the "alkanoyl group" is, for example, an alkanoyl group having a carbon number of 1 to 7 (e.g., 1 - 7, 1 - 6), such as, formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, butyryl, valeryl, pivaloyl) and the like.

[0215]

In compound (I'), unless otherwise specified, the "C_{1-6} alkanoyl group" is, for example, formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, butyryl, valeryl, pivaloyl) or the like.

[0216]

In compound (I'), unless otherwise specified, the "alkoxy group" is, for example, an alkoxy group having 1 to 6 carbon atoms (e.g., 1 - 6, 2 - 6, 1 - 4), such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, n-pentyloxy, n-hexyloxy and the like.

[0217]

In compound (I'), unless otherwise specified, the "C_{1-6} alkoxy group" is, for example, methoxy, ethoxy, n-propoxy,

isopropoxy, n-butoxy, tert-butoxy, n-pentyloxy, n-hexyloxy or the like.

[0218]

In compound (I'), unless otherwise specified, the "C_{2-6} alkoxy group" is, for example, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, n-pentyloxy, n-hexyloxy or the like.

[0219]

In compound (I'), unless otherwise specified, the "C_{1-4} alkoxy group" is, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy or the like.

[0220]

In compound (I'), unless otherwise specified, the "alkylene" is, for example, alkylene having a carbon number of 1 to 4 (e.g., 1 - 4, 1 - 3), such as $-CH_2-$, $-CH_2CH_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$, $-C(CH_3)_2CH_2-$, $-CH_2C(CH_3)_2-$ and the like.

[0221]

In compound (I'), unless otherwise specified, the "C_{1-4} alkylene" is, for example, $-CH_2-$, $-CH_2CH_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$, $-C(CH_3)_2CH_2-$, $-CH_2C(CH_3)_2-$ or the like.

[0222]

In compound (I'), unless otherwise specified, the "C_{1-3} alkylene" is, for example, $-CH_2-$, $-CH_2CH_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$ or the like.

[0223]

In compound (I'), unless otherwise specified, the "hydrocarbon group" of the "optionally substituted hydrocarbon group" is, for example, alkyl group, alkenyl group, alkynyl group, cycloalkyl group, cycloalkenyl group, cycloalkadienyl group, aryl group, aralkyl group, arylalkenyl group, cycloalkyl-alkyl group or the like, with preference given to C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{2-10} alkynyl group, C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group, C_{4-10} cycloalkadienyl group, C_{6-14} aryl group, C_{7-16} aralkyl group, C_{8-13} arylalkenyl

group, C_{3-10} cycloalkyl-C_{1-6} alkyl group and the like.

[0224]

The above-mentioned C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group and C_{4-10} cycloalkadienyl group may be each condensed with a benzene ring. Examples of the fused ring group include indanyl, dihydronaphthyl, tetrahydronaphthyl, fluorenyl and the like. In addition, bridged hydrocarbon group such as norbornanyl, adamantyl and the like can also be mentioned as the above-mentioned hydrocarbon group.

[0225]

Examples of the C_{8-13} arylalkenyl group include styryl and the like.

[0226]

Examples of the C_{3-10} cycloalkyl-C_{1-6} alkyl group include cyclopropylmethyl, cyclohexylmethyl and the like.

[0227]

The C_{1-10} alkyl group, C_{2-10} alkenyl group and C_{2-10} alkynyl group exemplified as the above-mentioned "hydrocarbon group" optionally have 1 to 3 substituents at substitutable positions.

[0228]

Examples of the substituent include

(1) a C_{3-10} cycloalkyl group (e.g., cyclopropyl, cyclohexyl) optionally substituted by 1 to 3 substituents selected from the group consisting of

halogen;

hydroxy;

carboxyl;

sulfo;

cyano;

azido;

nitro;

nitroso;

optionally halogenated C_{1-4} alkyl;

optionally halogenated C_{2-4} alkenyl;

optionally halogenated C_{2-4} alkynyl;

C_{3-7} cycloalkyl;

C_{6-14} aryl;

C_{7-16} aralkyl;

formyl;

optionally halogenated C_{1-6} alkyl-carbonyl;

optionally halogenated C_{1-6} alkoxy-carbonyl;

optionally halogenated C_{1-6} alkylsulfonyl;

carbamoyl;

carbamoyl mono- or di-substituted by optionally halogenated C_{1-6} alkyl;

mono- or di-C_{6-14} aryl-carbamoyl;

thiocarbamoyl optionally mono- or di-substituted by optionally halogenated C_{1-6} alkyl;

ureido optionally mono- or di-substituted by optionally halogenated C_{1-6} alkyl;

mono- or di-C_{6-14} aryl-ureido;

sulfamoyl optionally mono- or di-substituted by optionally halogenated C_{1-6} alkyl;

optionally halogenated C_{1-6} alkoxy;

optionally halogenated C_{2-6} alkenyloxy;

C_{3-10} cycloalkyloxy;

C_{7-16} aralkyloxy;

C_{6-14} aryloxy;

C_{1-6} alkyl-carbonyloxy;

C_{3-10} cycloalkyl-C_{1-6} alkoxy;

C_{1-6} alkylsulfonyloxy;

mercapto;

optionally halogenated C_{1-6} alkylthio;

C_{7-16} aralkylthio;

C_{6-14} arylthio;

C_{1-6} alkylsulfinyl;

oxo;

C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy);

hydroxyimino optionally substituted by C_{1-6} alkyl;

and the like (substituent group S);

(2) a C_{6-14} aryl group (e.g., phenyl, naphthyl) optionally substituted by 1 to 3 substituents selected from substituent group S;

(3) a heterocyclic group optionally substituted by 1 to 3 substituents selected from substituent group S;

(4) an amino group optionally substituted by 1 or 2 substituents selected from the group consisting of

C_{1-6} alkyl optionally substituted by substituent selected from the group consisting of halogen, hydroxy, C_{3-7} cycloalkyl, C_{1-6} alkylsulfonyl, C_{1-6} alkoxy and the like;

optionally halogenated C_{2-4} alkenyl;

optionally halogenated C_{2-4} alkynyl;

C_{3-7} cycloalkyl;

C_{6-14} aryl;

C_{7-16} aralkyl;

a 4- to 7-membered (preferably 5- or 6-membered) heterocyclic group (e.g., nonaromatic heterocyclic group such as morpholinyl and the like) containing, as a ring constitution atom besides carbon atom, 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom and nitrogen atom;

formyl;

C_{1-6} alkyl-carbonyl optionally substituted by substituent selected from the group consisting of halogen, hydroxy, C_{3-7} cycloalkyl, C_{1-6} alkylsulfonyl, C_{1-6} alkoxy and the like;

C_{1-6} alkoxy-carbonyl;

C_{6-14} aryl-carbonyl (e.g., benzoyl);

C_{7-16} aralkyl-carbonyl (e.g., benzylcarbonyl, phenethylcarbonyl);

C_{3-7} cycloalkyl-carbonyl;

C_{1-6} alkyl-carbamoyl (e.g., methylaminocarbonyl, ethylaminocarbonyl);

C_{6-14} aryl-carbamoyl (e.g., phenylaminocarbonyl, 1-naphthylaminocarbonyl, 2-naphthylaminocarbonyl);

C_{7-16} aralkyl-carbamoyl (e.g., benzylaminocarbonyl);

C_{1-6} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, isopropylsulfonyl);

C_{6-14} arylsulfonyl (e.g., benzenesulfonyl, toluenesulfonyl, 1-naphthalenesulfonyl, 2-naphthalenesulfonyl);

C_{7-16} aralkylsulfonyl (e.g., benzylsulfonyl); and the like (substituent group T);

(5) amidino group;

(6) optionally formylated or halogenated C_{1-6} alkyl-carbonyl group;

(7) optionally halogenated C_{1-6} alkoxy-carbonyl group;

(8) optionally halogenated C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl);

(9) carbamoyl group optionally substituted by 1 or 2 substituents selected from substituent group T;

(10) thiocarbamoyl group optionally mono- or di-substituted by optionally halogenated C_{1-6} alkyl group;

(11) ureido group optionally substituted by 1 or 2 substituents selected from substituent group T;

(12) sulfamoyl group optionally substituted by 1 or 2 substituents selected from substituent group T;

(13) carboxyl group;

(14) hydroxy group;

(15) C_{1-6} alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, carboxyl, C_{1-6} alkoxy and C_{1-6} alkoxy-carbonyl;

(16) optionally halogenated C_{2-6} alkenyloxy group (e.g., ethenyloxy);

(17) C_{3-10} cycloalkyloxy group (e.g., cyclohexyloxy);

(18) C_{7-16} aralkyloxy group (e.g., benzyloxy);

(19) C_{6-14} aryloxy group (e.g., phenyloxy, naphthyloxy);

(20) C_{1-6} alkyl-carbonyloxy group (e.g., acetyloxy, tert-butylcarbonyloxy);

(21) mercapto group;

(22) optionally halogenated C_{1-6} alkylthio group (e.g., methylthio, ethylthio);

(23) C_{7-16} aralkylthio group (e.g., benzylthio);
(24) C_{6-14} arylthio group (e.g., phenylthio, naphthylthio);
(25) sulfo group;
(26) cyano group;
(27) azido group;
(28) nitro group;
(29) nitroso group;
(30) halogen atom;
(31) C_{1-6} alkylsulfinyl group (e.g., methylsulfinyl);
(32) oxo group;
(33) C_{3-10} cycloalkyl-C_{1-6} alkoxy group (e.g., cyclopropylmethoxy);
(34) C_{1-3} alkylenedioxy group (e.g., methylenedioxy, ethylenedioxy);
(35) hydroxyimino group optionally substituted by C_{1-6} alkyl;
and the like (substituent group U). When the number of substituents is two or more, the respective substituents may be the same or different.

[0229]

The C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group, C_{4-10} cycloalkadienyl group, C_{6-14} aryl group, C_{7-16} aralkyl group, C_{8-13} arylalkenyl group and C_{3-10} cycloalkyl-C_{1-6} alkyl group exemplified as the above-mentioned "hydrocarbon group" optionally have 1 to 3 substituents at substitutable positions.

[0230]

Examples of the substituent include
(1) substituent selected from substituent group U;
(2) C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from substituent group U;
(3) C_{2-10} alkenyl group (e.g., ethenyl, 1-propenyl) optionally substituted by 1 to 3 substituents selected from substituent group U;
(4) C_{7-16} aralkyl group (e.g., benzyl) optionally substituted by 1 to 3 substituents selected from substituent group U; and the like (substituent group V). When the number of substituents is

two or more, the respective substituents may be the same or different.

[0231]

In compound (I'), unless otherwise specified, examples of the "heterocyclic group" of the "optionally substituted heterocyclic group" include an aromatic heterocyclic group and a non-aromatic heterocyclic group.

[0232]

Examples of the "aromatic heterocyclic group" include a 4- to 7-membered (preferably 5- or 6-membered) monocyclic aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atoms, 1 to 4 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom, and a fused aromatic heterocyclic group. Examples of the fused aromatic heterocyclic group include a group derived from a fused ring, wherein a ring corresponding to such 4- to 7-membered monocyclic aromatic heterocyclic group, and 1 or 2 rings selected from the group consisting of a 5- or 6-membered aromatic heterocycle containing 1 or 2 nitrogen atoms, a 5-membered aromatic heterocycle containing one sulfur atom and a benzene ring and the like are fused, and the like.

[0233]

Preferable examples of the aromatic heterocyclic group include

monocyclic aromatic heterocyclic groups such as furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrazinyl (e.g., 2-pyrazinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl),

isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (e.g., 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl), thiadiazolyl (e.g., 1,3,4-thiadiazol-2-yl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl, tetrazol-5-yl), triazinyl (e.g., 1,2,4-triazin-1-yl, 1,2,4-triazin-3-yl) and the like; fused aromatic heterocyclic groups such as quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 6-quinolyl), isoquinolyl (e.g., 3-isoquinolyl), quinazolyl (e.g., 2-quinazolyl, 4-quinazolyl), quinoxalyl (e.g., 2-quinoxalyl, 6-quinoxalyl), benzofuryl (e.g., 2-benzofuryl, 3-benzofuryl), benzothienyl (e.g., 2-benzothienyl, 3-benzothienyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzisoxazolyl (e.g., 7-benzisoxazolyl), benzothiazolyl (e.g., 2-benzothiazolyl), benzimidazolyl (e.g., benzimidazol-1-yl, benzimidazol-2-yl, benzimidazol-5-yl), benzotriazolyl (e.g., 1H-1,2,3-benzotriazol-5-yl), indolyl (e.g., indol-1-yl, indol-2-yl, indol-3-yl, indol-5-yl), indazolyl (e.g., 1H-indazol-3-yl), pyrrolopyrazinyl (e.g., 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyrazin-6-yl), imidazopyridinyl (e.g., 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 2H-imidazo[1,2-a]pyridin-3-yl), imidazopyrazinyl (e.g., 1H-imidazo[4,5-b]pyrazin-2-yl), pyrazolopyridinyl (e.g., 1H-pyrazolo[4,3-c]pyridin-3-yl), pyrazolothienyl (e.g., 2H-pyrazolo[3,4-b]thiophen-2-yl), pyrazolotriazinyl (e.g., pyrazolo[5,1-c][1,2,4]triazin-3-yl) and the like; and the like.

[0234]

Examples of the "non-aromatic heterocyclic group" include a 4- to 7-membered (preferably 5- or 6-membered) monocyclic non-aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atoms, 1 to 4 heteroatoms

selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom, and a fused non-aromatic heterocyclic group. Examples of the fused non-aromatic heterocyclic group include a group derived from a fused ring, wherein a ring corresponding to such 4- to 7-membered monocyclic non-aromatic heterocyclic group, and 1 or 2 rings selected from the group consisting of a 5- or 6-membered heterocycle containing 1 or 2 nitrogen atoms, a 5-membered heterocycle containing one sulfur atom and a benzene ring and the like are fused, and the like.

[0235]

Preferable examples of the non-aromatic heterocyclic group include

monocyclic non-aromatic heterocyclic groups such as oxetanyl (e.g., 2-oxetanyl, 3-oxetanyl), pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl), piperidinyl (e.g., piperidino, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), morpholinyl (e.g., morpholino), thiomorpholinyl (e.g., thiomorpholino), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl, 3-piperazinyl), hexamethyleniminyl (e.g., hexamethylenimin-1-yl), oxazolidinyl (e.g., oxazolidin-2-yl), thiazolidinyl (e.g., thiazolidin-2-yl), imidazolidinyl (e.g., imidazolidin-2-yl, imidazolidin-3-yl), oxazolinyl (e.g., oxazolin-2-yl), thiazolinyl (e.g., thiazolin-2-yl), imidazolinyl (e.g., imidazolin-2-yl, imidazolin-3-yl), dioxolyl (e.g., 1,3-dioxol-4-yl), dioxolanyl (e.g., 1,3-dioxolan-4-yl), dihydrooxadiazolyl (e.g., 4,5-dihydro-1,2,4-oxadiazol-3-yl), 2-thioxo-1,3-oxazolidin-5-yl, pyranyl (e.g., 4-pyranyl), tetrahydropyranyl (e.g., 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl), thiopyranyl (e.g., 4-thiopyranyl), tetrahydrothiopyranyl (e.g., 2-tetrahydrothiopyranyl, 3-tetrahydrothiopyranyl, 4-tetrahydrothiopyranyl), 1-oxidotetrahydrothiopyranyl (e.g., 1-oxidotetrahydrothiopyran-4-yl), 1,1-dioxidotetrahydrothiopyranyl (e.g., 1,1-

dioxidotetrahydrothiopyran-4-yl), tetrahydrofuryl (e.g., tetrahydrofuran-3-yl, tetrahydrofuran-2-yl), pyrazolidinyl (e.g., pyrazolidin-1-yl, pyrazolidin-3-yl), pyrazolinyl (e.g., pyrazolin-1-yl), tetrahydropyrimidinyl (e.g., tetrahydropyrimidin-1-yl), dihydrotriazolyl (e.g., 2,3-dihydro-1H-1,2,3-triazol-1-yl), tetrahydrotriazolyl (e.g., 2,3,4,5-tetrahydro-1H-1,2,3-triazol-1-yl) and the like; fused non-aromatic heterocyclic groups such as dihydroindolyl (e.g., 2,3-dihydro-1H-indol-1-yl), dihydroisoindolyl (e.g., 1,3-dihydro-2H-isoindol-2-yl), dihydrobenzofuranyl (e.g., 2,3-dihydro-1-benzofuran-5-yl), dihydrobenzodioxinyl (e.g., 2,3-dihydro-1,4-benzodioxinyl), dihydrobenzodioxepinyl (e.g., 3,4-dihydro-2H-1,5-benzodioxepinyl), tetrahydrobenzofuranyl (e.g., 4,5,6,7-tetrahydro-1-benzofuran-3-yl), chromenyl (e.g., 4H-chromen-2-yl, 2H-chromen-3-yl), dihydroquinolinyl (e.g., 1,2-dihydroquinolin-4-yl), tetrahydroquinolinyl (e.g., 1,2,3,4-tetrahydroquinolin-4-yl), dihydroisoquinolinyl (e.g., 1,2-dihydroisoquinolin-4-yl), tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydroisoquinolin-4-yl), dihydrophthalazinyl (e.g., 1,4-dihydrophthalazin-4-yl) and the like; and the like.

[0236]

The "heterocyclic group" of the "optionally substituted heterocyclic group" may have 1 to 3 substituents at the substitutable positions. Examples of such substituent include substituents selected from the group consisting of substituent group V. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

[0237]

In compound (I'), unless otherwise specified, the "aliphatic hydrocarbon group" of the "optionally substituted aliphatic hydrocarbon group" is, for example, a straight chain or branched aliphatic hydrocarbon group having a carbon number of 1 - 10 (preferably, 1 - 8). Examples of the "aliphatic

hydrocarbon group" include C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{2-10} alkynyl group and C_{3-10} cycloalkyl group (each group is as defined above).

[0238]

The "aliphatic hydrocarbon group" is optionally substituted by 1 to 3 substituents selected from substituent group V, particularly, halogen, hydroxy, C_{1-4} alkoxy, C_{1-4} alkyl-carbonyl, carboxy, C_{1-4} alkoxy-carbonyl, cyano, carbamoyl, sulfamoyl, nitro, amino, C_{1-4} alkyl-carbonylamino, C_{1-4} alkoxy-carbonylamino and C_{1-4} alkylsulfonylamino. When the substituents are two, the respective substituents may be the same or different.

[0239]

In compound (I'), unless otherwise specified, the "acyl group" is, for example, $-COR^{Y1}$, $-CO-OR^{Y1}$, $-SO_2R^{Y1}$, $-SOR^{Y1}$, $-PO(OR^{Y1})(OR^{Y2})$ [R^{Y1} and R^{Y2} are the same or different and each is hydrogen atom, optionally substituted hydrocarbon group, or optionally substituted heterocyclic group] or the like.

[0240]

In compound (I'), unless otherwise specified, the "amino group" of the "optionally substituted amino group", the "carbamoyl group" of the "optionally substituted carbamoyl group", the "ureido group" of the "optionally substituted ureido group", and the "sulfamoyl group" of the "optionally substituted sulfamoyl group" optionally have 1 or 2 substituents at substitutable positions. Examples of the substituent include optionally substituted hydrocarbon group, optionally substituted heterocyclic group, acyl group and the like, with preference given to 1 or 2 substituents selected from the group consisting of substituent group T. When the substituents are two, the respective substituents may be the same or different.

[0241]

When the nitrogen atom constituting the above-mentioned amino group, carbamoyl group, ureido group, or sulfamoyl group

is substituted by two substituents, these substituents may form, together with the adjacent nitrogen atom, a nitrogen-containing heterocycle. Examples of the "nitrogen-containing heterocycle" include a 3- to 8-membered nitrogen-containing heterocycle containing, as a ring constituting atom besides carbon atom, at least one nitrogen atom, and further, 1 or 2 hetero atoms selected from the group consisting of oxygen atom, sulfur atom and nitrogen atom. Preferable examples of the nitrogen-containing heterocycle include 5- or 6-membered cyclic amine (e.g., 1-pyrrolidine, piperidine, 1-piperazine, morpholine) optionally containing an oxygen atom.

[0242]

In compound (I'), unless otherwise specified, the "imino group" of the "optionally substituted imino group" optionally have 1 or 2 substituents at substitutable positions. Examples of the substituent include optionally substituted hydrocarbon group, optionally substituted heterocyclic group, acyl group and the like, with preference given to the substituents of substituent group T. When the substituents are two, the respective substituents may be the same or different.

[0243]

In compound (I'), unless otherwise specified, the "optionally substituted group bonded via a carbon atom, nitrogen atom or oxygen atom" is, for example, a group represented by the formula $-X^x-R^x$, amino group or hydroxy group.

[0244]

In the above-mentioned formula, X^x is a bond, $-NR^Y-$ (R^Y is a hydrogen atom or a C_{1-6} alkyl group), or -O-.

[0245]

In the above-mentioned the formula, R^x is cyano group, or C_{1-8} alkyl group, C_{2-8} alkenyl group, C_{2-8} alkynyl group, carbamoyl group, C_{1-8} alkyl-carbonyl group, C_{3-8} cycloalkyl group, C_{6-18} aryl group, C_{6-18} aryl-C_{1-4} alkyl group, C_{6-18} aryl-carbonyl group, C_{6-18} aryl-C_{1-4} alkyl-carbonyl group, heterocyclic group, heterocyclyl-C_{1-4} alkyl group, heterocyclylcarbonyl group or

heterocyclyl-C_{1-4} alkyl-carbonyl group, each of which is optionally substituted.

[0246]

In the above-mentioned the formula, the "C_{1-8} alkyl group", "C_{2-8} alkenyl group", "C_{2-8} alkynyl group", "carbamoyl group", "C_{1-8} alkyl-carbonyl group", "C_{3-8} cycloalkyl group", "C_{6-18} aryl group", "C_{6-18} aryl-C_{1-4} alkyl group", "C_{6-18} aryl-carbonyl group", "C_{6-18} aryl-C_{1-4} alkyl-carbonyl group", "heterocyclic group", "heterocyclyl-C_{1-4} alkyl group", "heterocyclylcarbonyl group" and "heterocyclyl-C_{1-4} alkyl-carbonyl group" for R^x are optionally substituted by one or more (preferably 1 to 5, more preferably 1 to 3) substituents selected from the group consisting of, for example,

(a) halogen atom,

(b) oxo group,

(c) optionally halogenated C_{1-4} alkyl group,

(d) $-(CH_2)_m-Q^x$ group,

(e) $-(CH_2)_m-Z^{1x}-$ optionally halogenated C_{1-4} alkyl group,

(f) $-(CH_2)_m-Z^{1x}-C_{3-8}$ cycloalkyl group,

(g) $-(CH_2)_m-Z^{2x}-(CH_2)_n-Q^x$ group,

(h) $-(CH_2)_m-Z^{2x}-(CH_2)_n-Z^{1x}-$ optionally halogenated C_{1-4} alkyl group,

(i) $-(CH_2)_m-Z^{2x}-(CH_2)_n-Z^{1x}-C_{3-8}$ cycloalkyl group,

(j) $-(CH_2)_m-Z^{1x}-$(optionally substituted heterocyclic group) (preferably, 5- to 8-membered heterocyclic group having 1 to 3 hetero atoms selected from the group consisting of nitrogen atom, oxygen atom, and optionally oxidized sulfur atom),

(k) $-(CH_2)_m-Z^{2x}-C_{1-4}$ alkoxy group, and

(l) $-(CH_2)_m-Z^{2x}-(CH_2)_n-Z^{1x}-(CH_2)_n-Z^{1x}-C_{1-4}$ alkyl group (substituent group X).

[0247]

R^Y is preferably a hydrogen atom or methyl, particularly preferably a hydrogen atom.

[0248]

In the above-mentioned the formula,

m is an integer of 0 to 4,

n is an integer of 1 to 4,

Q^x is hydroxy, carboxy, cyano, nitro, $-NR^{1x}R^{2x}$, $-CONR^{1x}R^{2x}$ or $-SO_2NR^{1x}R^{2x}$,

Z^{1x} is $-O-$, $-CO-$, $-C(OH)R^{3x}-$, $-C(=N-OR^{3x})-$, $-S-$, $-SO-$, $-SO_2-$, $-N(COR^{3x})-$, $-N(CO_2R^{4x})-$, $-N(SO_2R^{4x})-$, $-CO-O-$, $-O-CO-$, $-CO-NR^{3x}-$, $-NR^{3x}-CO-$, $-NR^{3x}-CO_2-$, $-NR^{3x}-CO-NH-$, $-NR^{3x}-SO_2-$ or $-NR^{3x}-C(=NH)-NH-$, and

Z^{2x} is $-O-$, $-CO-$, $-C(OH)R^{3x}-$, $-C(=N-OR^{3x})-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{3x}-$, $-N(COR^{3x})-$, $-N(CO_2R^{4x})-$, $-N(SO_2R^{4x})-$, $-CO-O-$, $-O-CO-$, $-CO-NR^{3x}-$, $-NR^{3x}-CO-$, $-NR^{3x}-CO_2-$, $-NR^{3x}-CO-NH-$, $-NR^{3x}-C(=NH)-NH-$, $-NR^{3x}-SO_2-$ or $-SO_2-NR^{3x}-$.

[0249]

In addition, $-(CH_2)_m-$ and $-(CH_2)_n-$ in the above-mentioned formula are, for example, optionally substituted by one or more (preferably 1 to 5, more preferably 1 to 3) substituents selected from halogen, optionally halogenated C_{1-4} alkyl and hydroxy, and when m or n is two or more, $-CH_2CH_2-$ of $-(CH_2)_m-$ or $-(CH_2)_n-$ may be replaced with $-CH=CH-$ or $-C\equiv C-$.

[0250]

In the above-mentioned formula, R^{1x} and R^{2x} are the same or different and each is hydrogen atom or C_{1-4} alkyl, or R^{1x} and R^{2x} may be bonded to form a ring together with nitrogen atom. In the above-mentioned formula, R^{3x} is a hydrogen atom or C_{1-4} alkyl and R^{4x} is C_{1-4} alkyl.

[0251]

When R^{1x} and R^{2x} are bonded to form a ring together with nitrogen atom, the nitrogen-containing heterocycle is, for example, a 3- to 8-membered (preferably 5- or 6-membered) saturated or unsaturated (preferably saturated) aliphatic heterocycle such as azetidine, pyrrolidine, piperidine, homopiperidine, heptamethylenimine, morpholine, thiomorpholine, piperazine, homopiperazine and the like.

[0252]

In compound (I'), unless otherwise specified, "optionally

substituted group bonded via a carbon atom or a sulfur atom" is, for example, C_{1-8} alkyl group, C_{2-8} alkenyl group, C_{2-8} alkynyl group, carbamoyl group, C_{1-8} alkyl-carbonyl group, C_{1-8} alkylthio group, C_{1-8} alkylsulfonyl group, C_{3-8} cycloalkyl group, C_{6-18} aryl group, C_{6-18} aryl-C_{1-4} alkyl group, C_{6-18} aryl-carbonyl group, C_{6-18} aryl-C_{1-4} alkyl-carbonyl group, C_{6-18} arylthio group, C_{6-18} arylsulfonyl group, heterocyclic group, heterocyclyl-C_{1-4} alkyl group, heterocyclylcarbonyl group, heterocyclyl-C_{1-4} alkyl-carbonyl group, heterocyclylthio group, heterocyclyl-C_{1-4} alkylthio group, each of which is optionally substituted, or the like.

[0253]

The "C_{1-8} alkyl group", "C_{2-8} alkenyl group", "C_{2-8} alkynyl group", "carbamoyl group", "C_{1-8} alkyl-carbonyl group", "C_{1-8} alkylthio group", "C_{1-8} alkylsulfonyl group", "C_{3-8} cycloalkyl group", "C_{6-18} aryl group", "C_{6-18} aryl-C_{1-4} alkyl group", "C_{6-18} aryl-carbonyl group", "C_{6-18} aryl-C_{1-4} alkyl-carbonyl group", "C_{6-18} arylthio group", "C_{6-18} arylsulfonyl group", "heterocyclic group", "heterocyclyl-C_{1-4} alkyl group", "heterocyclylcarbonyl group", "heterocyclyl-C_{1-4} alkyl-carbonyl group", "heterocyclylthio group" and "heterocyclyl-C_{1-4} alkylthio group" are optionally substituted by one or more (preferably 1 to 5, more preferably 1 to 3) substituents selected from, for example, the above-mentioned substituent group X.

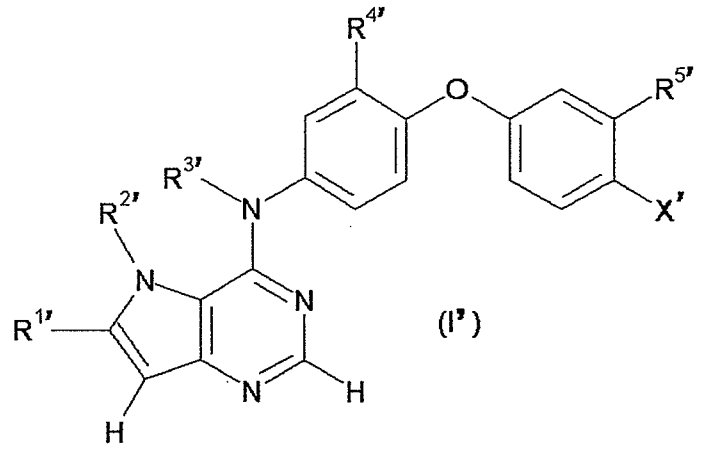
[0254]

[Compound (I')]

[0255]

The present invention provides a compound represented by the formula (I') (compound (I')) or a salt thereof.

[0256]



(I')

[0257]

wherein each symbol is as defined above.

[0258]

$R^{2'}$ is preferably a C_{1-6} alkyl group (particularly, ethyl group) substituted by a group represented by the formula "-$NR^{6'}$-CO-$CR^{7'}R^{8'}$-SO_2-C_{1-4} alkyl".

[0259]

In the formula, $R^{6'}$ is a hydrogen atom or a methyl group, $R^{7'}$ and $R^{8'}$ are the same or different and each is a hydrogen atom or a methyl group, and $R^{7'}$ and $R^{8'}$ are preferably methyl groups.

[0260]

$R^{3'}$ is preferably a hydrogen atom.

[0261]

The "halogen atom" for $R^{4'}$ is preferably a chlorine atom. The "C_{1-6} alkyl group" for $R^{4'}$ is preferably a methyl group. $R^{4'}$ is preferably a chlorine atom or a methyl group.

[0262]

The "halogen atom" for $R^{5'}$ is preferably a fluorine atom or a chlorine atom. The "C_{1-6} alkyl group" for $R^{5'}$ is preferably a methyl group. $R^{5'}$ is preferably a fluorine atom, a chlorine atom or a methyl group.

[0263]

The "halogen atom" for X' is preferably a fluorine atom. X' is preferably a hydrogen atom or a fluorine atom, more

preferably a hydrogen atom.

[0264]

A preferable embodiment of compound (I') is that wherein $R^{1'}$ is a hydrogen atom, $R^{2'}$ is a C_{1-6} alkyl group (particularly, ethyl group) substituted by a group represented by $-NR^{6'}-CO-CR^{7'}R^{8'}-SO_2-C_{1-4}$ alkyl wherein $R^{6'}$ is a hydrogen atom or a methyl group, and $R^{7'}$ and $R^{8'}$ are the same or different and each is a hydrogen atom or a methyl group,

$R^{3'}$ is a hydrogen atom,

$R^{4'}$ is a chlorine atom or a methyl group,

$R^{5'}$ is a fluorine atom, a chlorine atom or a methyl group, and

X' is a hydrogen atom or a fluorine atom (preferably, a hydrogen atom).

[0265]

A more preferable embodiment of compound (I') is that wherein

$R^{1'}$ is a hydrogen atom,

$R^{2'}$ is a C_{1-6} alkyl group (particularly, ethyl group) substituted by a group represented by $-NR^{6'}-CO-CR^{7'}R^{8'}-SO_2-C_{1-4}$ alkyl wherein $R^{6'}$ is a hydrogen atom or a methyl group, and $R^{7'}$ and $R^{8'}$ are methyl groups,

$R^{3'}$ is a hydrogen atom,

$R^{4'}$ is a chlorine atom or a methyl group,

$R^{5'}$ is a fluorine atom, a chlorine atom or a methyl group, and

X' is a hydrogen atom or a fluorine atom (preferably, a hydrogen atom).

[0266]

As the salts of the compound represented by each of the above-mentioned formulas, for example, metal salt, ammonium salt, salts with organic base, salts with inorganic acid, salts with organic acid, salts with basic or acidic amino acid and the like can be mentioned.

[0267]

As preferable examples of the metal salt, for example, alkali metal salts such as sodium salt, potassium salt and the

like; alkaline earth metal salts such as calcium salt, magnesium salt, barium salt and the like; aluminum salt and the like can be mentioned.

[0268]

As preferable examples of the salts with organic base, for example, salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, tromethamine[tris(hydroxymethyl)methylamine], t-butylamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like can be mentioned.

[0269]

As preferable examples of salts with inorganic acid, for example, salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like can be mentioned.

[0270]

As preferable examples of the salts with organic acid, for example, salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like can be mentioned.

[0271]

As preferable examples of the salts with basic amino acid, for example, salts with arginine, lysine, ornithine and the like can be mentioned.

[0272]

As preferable examples of the salts with acidic amino acid, for example, salts with aspartic acid, glutamic acid and the like can be mentioned.

[0273]

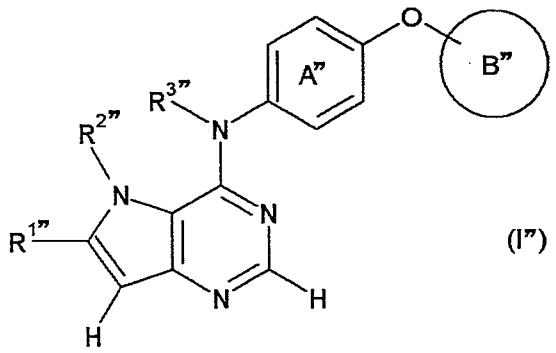
Of these, pharmaceutically acceptable salts are preferable. For example, when a compound contains an acidic functional group, inorganic salts such as alkali metal salts (e.g., sodium salt, potassium salt etc.), alkaline earth metal

salts (e.g., calcium salt, magnesium salt, barium salt etc.) and the like, ammonium salt and the like, and when a compound contains a basic functional group, for example, salts with inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like, or salts with organic acid such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like can be mentioned.

[0274]

Each term used in the present specification is explained in the following by referring to the compound of the formula (I″):

[0275]



(I″)

[0276]

wherein

$R^{1''}$ is a hydrogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

$R^{2''}$ is a hydrogen atom, or an optionally substituted group bonded via a carbon atom or a sulfur atom, or

$R^{1''}$ and $R^{2''}$, or $R^{2''}$ and $R^{3''}$ are optionally bonded to each other to form an optionally substituted ring structure;

$R^{3''}$ is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or

$R^{3''}$ is optionally bonded to a carbon atom of ring A″ to form an optionally substituted ring structure;

ring A″ is an optionally substituted benzene ring;

ring B" is (i) an optionally substituted fused ring, or

(ii) a pyridine ring having optionally substituted carbamoyl wherein the pyridine ring is optionally further substituted; (hereinafter sometimes to be abbreviated as compound (I"))

or a salt thereof.

[0277]

$R^{1"}$ is a hydrogen atom, a halogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom.

Examples of the "halogen atom" for $R^{1"}$ include a fluorine atom, a chlorine atom, a bromine atom and an iodine atom.

[0278]

Of the "optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom" for $R^{1"}$, examples of the "optionally substituted group bonded via a carbon atom" include cyano, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, optionally substituted carbamoyl, optionally substituted C_{1-8} alkyl-carbonyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-18} aryl, optionally substituted C_{6-18} aryl-C_{1-4} alkyl, optionally substituted C_{6-18} aryl-carbonyl, optionally substituted C_{6-18} aryl-C_{1-4} alkyl-carbonyl, an optionally substituted heterocyclic group, optionally substituted heterocyclyl-C_{1-4} alkyl, optionally substituted heterocyclyl-carbonyl and optionally substituted heterocyclyl-C_{1-4} alkyl-carbonyl.

[0279]

Examples of the "C_{1-8} alkyl" of the above-mentioned "optionally substituted C_{1-8} alkyl" include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, heptyl, octyl and the like.

[0280]

The "C_{1-8} alkyl" of the above-mentioned "optionally substituted C_{1-8} alkyl" may have one or more (preferably 1 to 5, more preferably 1 to 3) substituents at the substitutable positions. Such substituent is selected from the group consisting of

(a) a halogen atom,

(b) oxo,

(c) optionally-halogenated C_{1-4} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl),

(d) C_{3-8} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl etc.),

(e) $-(CH_2)_m-Q''$ group,

(f) $-(CH_2)_m-Z^{1''}-$(C_{1-4} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl) optionally substituted by substituent(s) selected from hydroxy, a halogen atom, cyano, C_{1-4} alkoxy, amino and di-C_{1-4} alkylamino),

(g) $-(CH_2)_m-Z^{1''}-$(C_{3-8} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl etc.) optionally substituted by substituent(s) selected from hydroxyl and cyano),

(h) $-(CH_2)_m-Z^{1''}-$(C_{6-10} aryl (e.g., phenyl etc.) optionally substituted by C_{1-4} alkyl optionally substituted by halogen atom(s)),

(i) $-(CH_2)_m-Z^{2''}-(CH_2)_n-Q''$ group,

(j) $-(CH_2)_m-Z^{2''}-(CH_2)_n-Z^{1''}-C_{1-4}$ alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl),

(k) $-(CH_2)_m-Z^{2''}-(CH_2)_n-Z^{1''}-C_{3-8}$ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl etc.),

(l) $-(CH_2)_m-Z^{1''}-$(a heterocyclic group optionally substituted by substituent(s) selected from C_{1-4} alkyl, hydroxy and amino (preferably a 5- to 8-membered heterocyclic group having 1 to 3 heteroatoms selected from a nitrogen atom, an oxygen atom and an optionally oxidized sulfur atom)),

(m) $-(CH_2)_m-Z^{2''}-(CH_2)_n-$(a heterocyclic group (preferably a 5- to

8-membered heterocyclic group having 1 to 3 heteroatoms selected from a nitrogen atom, an oxygen atom and an optionally oxidized sulfur atom) optionally substituted by C_{1-4} alkyl),

(n) $-(CH_2)_m-Z^{2''}-C_{1-4}$ alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy),

(o) $-(CH_2)_m-Z^{2''}-(CH_2)_n-Z^{1''}-(CH_2)_n-Z^{1''}-C_{1-4}$ alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl), and

(p) 3- to 6-membered cyclic amino optionally substituted by substituent(s) selected from C_{1-4} alkyl and oxo

(hereinafter sometimes to be referred to as substituent group X). When the number of the substituents is 2 or more, the respective substituents may be the same or different.

[0281]

In the above-mentioned formulas,

m is an integer of 0 to 4;

n is an integer of 1 to 4;

Q'' is hydroxy, carboxy, cyano, nitro, $-NR^{11''}R^{12''}$, $-CONR^{11''}R^{12''}$ or $-SO_2NR^{11''}R^{12''}$;

$Z^{1''}$ is $-O-$, $-CO-$, $-C(OH)R^{13''}-$, $-C(=N-OR^{13''})-$, $-S-$, $-SO-$, $-SO_2-$, $-N(COR^{13''})-$, $-N(CO_2R^{14''})-$, $-N(SO_2R^{14''})-$, $-CO-O-$, $-O-CO-$, $-CO-NR^{13''}-$, $-NR^{13''}-CO-$, $-NR^{13''}-CO_2-$, $-NR^{13''}-CO-NH-$, $-NR^{13''}-SO_2-$ or $-NR^{13''}-C(=NH)-NH-$; and

$Z^{2''}$ is $-O-$, $-CO-$, $-C(OH)R^{13''}-$, $-C(=N-OR^{13''})-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{13''}-$, $-N(COR^{13''})-$, $-N(CO_2R^{14''})-$, $-N(SO_2R^{14''})-$, $-CO-O-$, $-O-CO-$, $-CO-NR^{13''}-$, $-NR^{13''}-CO-$, $-NR^{13''}-CO_2-$, $-NR^{13''}-CO-NH-$, $-NR^{13''}-C(=NH)-NH-$, $-NR^{13''}-SO_2-$ or $-SO_2-NR^{13''}-$.

[0282]

In addition, $-(CH_2)_m-$ and $-(CH_2)_n-$ in the above-mentioned formulas are optionally substituted by, for example, one or more (preferably 1 to 5, more preferably 1 to 3) substituents selected from halogen, optionally halogenated C_{1-4} alkyl and hydroxy. When m or n is not less than 2, a subset $-CH_2CH_2-$ of $-(CH_2)_m-$ and $-(CH_2)_n-$ may be replaced by $-CH=CH-$ or $-C\equiv C-$.

[0283]

In the above-mentioned formulas, $R^{11''}$ and $R^{12''}$ are the same or different and each is a hydrogen atom or C_{1-4} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl), or $R^{11''}$ and $R^{12''}$ may be bonded to form a ring together with the nitrogen atom.

[0284]

In addition, in the above-mentioned formulas, $R^{13''}$ is a hydrogen atom or C_{1-4} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl), and $R^{14''}$ is C_{1-4} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl).

[0285]

When $R^{11''}$ and $R^{12''}$ are bonded to form a ring together with the nitrogen atom, Examples of the nitrogen-containing heterocyclic group include a 3- to 8-membered (preferably 5- or 6-membered) saturated or unsaturated (preferably saturated) aliphatic heterocycle such as azetidine, pyrrolidine, piperidine, homopiperidine, heptamethylenimine, morpholine, thiomorpholine, piperazine, homopiperazine and the like.

[0286]

Examples of the "C_{2-8} alkenyl" of the above-mentioned "optionally substituted C_{2-8} alkenyl" include ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl, 5-hexenyl, 1-heptenyl, 1-octenyl and the like.

[0287]

The "C_{2-8} alkenyl" of the above-mentioned "optionally substituted C_{2-8} alkenyl" may have one or more (preferably 1 to 5, more preferably 1 to 3) substituents at the substitutable positions. Examples of such substituent include substituents selected from substituent group X. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

[0288]

Examples of the "C_{2-8} alkynyl" of the above-mentioned "optionally substituted C_{2-8} alkynyl" include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 1-octynyl and the like.

[0289]

The "C_{2-8} alkynyl" of the above-mentioned "optionally substituted C_{2-8} alkynyl" may have one or more (preferably 1 to 5, more preferably 1 to 3) substituents at the substitutable positions. Examples of such substituent include substituents selected from substituent group X. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

[0290]

The "carbamoyl" of the above-mentioned "optionally substituted carbamoyl" may have 1 or 2 substituents at the substitutable positions. Examples of such substituent include substituents selected from substituent group X. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

[0291]

Examples of the "C_{1-8} alkyl-carbonyl" of the above-mentioned "optionally substituted C_{1-8} alkyl-carbonyl" include acetyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, butylcarbonyl, isobutylcarbonyl, sec-butylcarbonyl, tert-butylcarbonyl, pentylcarbonyl, isopentylcarbonyl, neopentylcarbonyl, 1-ethylpropylcarbonyl, hexylcarbonyl, isohexylcarbonyl, 1,1-dimethylbutylcarbonyl, 2,2-dimethylbutylcarbonyl, 3,3-dimethylbutylcarbonyl, 2-ethylbutylcarbonyl, heptylcarbonyl, octylcarbonyl and the like.

[0292]

The "C_{1-8} alkyl-carbonyl" of the above-mentioned "optionally substituted C_{1-8} alkyl-carbonyl" may have one or

more (preferably 1 to 5, more preferably 1 to 3) substituents at the substitutable positions. Examples of such substituent include substituents selected from substituent group X. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

[0293]

Examples of the "C_{3-8} cycloalkyl" of the above-mentioned "optionally substituted C_{3-8} cycloalkyl" include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

[0294]

The "C_{3-8} cycloalkyl" of the above-mentioned "optionally substituted C_{3-8} cycloalkyl" may have one or more (preferably 1 to 5, more preferably 1 to 3) substituents at the substitutable positions. Examples of such substituent include substituents selected from the below-mentioned substituent group V. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

[0295]

Examples of the "C_{6-18} aryl" of the above-mentioned "optionally substituted C_{6-18} aryl" include phenyl, naphthyl, anthryl, phenanthryl, acenaphthyl, biphenylyl and the like.

[0296]

The "C_{6-18} aryl" of the above-mentioned "optionally substituted C_{6-18} aryl" may have one or more (preferably 1 to 5, more preferably 1 to 3) substituents at the substitutable positions. Examples of such substituent include substituents selected from the below-mentioned substituent group V. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

[0297]

Examples of the "C_{6-18} aryl-C_{1-4} alkyl" of the above-mentioned "optionally substituted C_{6-18} aryl-C_{1-4} alkyl" include benzyl, phenethyl, phenylpropyl, naphthylmethyl, biphenylylmethyl and the like.

[0298]

The "C_{6-18} aryl-C_{1-4} alkyl" of the above-mentioned "optionally substituted C_{6-18} aryl-C_{1-4} alkyl" may have one or more (preferably 1 to 5, more preferably 1 to 3) substituents at the substitutable positions. Examples of such substituent include substituents selected from the below-mentioned substituent group V. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

[0299]

Examples of the "C_{6-18} aryl-carbonyl" of the above-mentioned "optionally substituted C_{6-18} aryl-carbonyl" include phenylcarbonyl, naphthylcarbonyl, anthrylcarbonyl, phenanthrylcarbonyl, acenaphthylcarbonyl, biphenylylcarbonyl and the like.

[0300]

The "C_{6-18} aryl-carbonyl" of the above-mentioned "optionally substituted C_{6-18} aryl-carbonyl" may have one or more (preferably 1 to 5, more preferably 1 to 3) substituents at the substitutable positions. Examples of such substituent include substituents selected from the below-mentioned substituent group V. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

[0301]

Examples of the "C_{6-18} aryl-C_{1-4} alkyl-carbonyl" of the above-mentioned "optionally substituted C_{6-18} aryl-C_{1-4} alkyl-carbonyl" include benzylcarbonyl, phenethylcarbonyl, phenylpropylcarbonyl, naphthylmethylcarbonyl, biphenylylmethylcarbonyl and the like.

[0302]

The "C_{6-18} aryl-C_{1-4} alkyl-carbonyl" of the above-mentioned "optionally substituted C_{6-18} aryl-C_{1-4} alkyl-carbonyl" may have one or more (preferably 1 to 5, more preferably 1 to 3) substituents at the substitutable positions. Examples of such

substituent include substituents selected from the below-mentioned substituent V. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

[0303]

Examples of the "heterocyclic group" of the above-mentioned "optionally substituted heterocyclic group" include an aromatic heterocyclic group and a non-aromatic heterocyclic group.

[0304]

Here, examples of the "aromatic heterocyclic group" include a 4- to 7-membered (preferably 5- or 6-membered) monocyclic aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atoms, 1 to 4 heteroatoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and a fused aromatic heterocyclic group. Examples of the fused aromatic heterocyclic group include a group derived from a fused ring wherein a ring corresponding to such 4- to 7-membered monocyclic aromatic heterocyclic group, and 1 or 2 rings selected from a 5- or 6-membered aromatic heterocycle containing 1 or 2 nitrogen atoms, a 5-membered aromatic heterocycle containing one sulfur atom and a benzene ring and the like are condensed, and the like.

[0305]

Preferable examples of the aromatic heterocyclic group include

monocyclic aromatic heterocyclic groups such as

furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrazinyl (e.g., 2-pyrazinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl),

thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (e.g., 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl), thiadiazolyl (e.g., 1,3,4-thiadiazol-2-yl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl, tetrazol-5-yl), triazinyl (e.g., 1,2,4-triazin-1-yl, 1,2,4-triazin-3-yl) and the like;
fused aromatic heterocyclic groups such as
quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 6-quinolyl), isoquinolyl (e.g., 3-isoquinolyl), quinazolyl (e.g., 2-quinazolyl, 4-quinazolyl), quinoxalyl (e.g., 2-quinoxalyl, 6-quinoxalyl), benzofuryl (e.g., 2-benzofuryl, 3-benzofuryl), benzothienyl (e.g., 2-benzothienyl, 3-benzothienyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzisoxazolyl (e.g., 7-benzisoxazolyl), benzothiazolyl (e.g., 2-benzothiazolyl), benzimidazolyl (e.g., benzimidazol-1-yl, benzimidazol-2-yl, benzimidazol-5-yl), benzotriazolyl (e.g., 1H-1,2,3-benzotriazol-5-yl), indolyl (e.g., indol-1-yl, indol-2-yl, indol-3-yl, indol-5-yl), indazolyl (e.g., 1H-indazol-3-yl), pyrrolopyrazinyl (e.g., 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyrazin-6-yl), pyrrolopyrimidinyl (e.g., 1H-pyrrolo[2,3-d]pyrimidin-2-yl, 1H-pyrrolo[2,3-d]pyrimidin-6-yl), imidazopyridinyl (e.g., 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 2H-imidazo[1,2-a]pyridin-3-yl), imidazopyrazinyl (e.g., 1H-imidazo[4,5-b]pyrazin-2-yl), pyrazolopyridinyl (e.g., 1H-pyrazolo[4,3-c]pyridin-3-yl), pyrazolothienyl (e.g., 2H-pyrazolo[3,4-b]thiophen-2-yl), pyrazolotriazinyl (e.g., pyrazolo[5,1-c][1,2,4]triazin-3-yl) and the like;
and the like.

[0306]

Examples of the "non-aromatic heterocyclic group" include

a 4- to 7-membered (preferably 5- or 6-membered) monocyclic non-aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atoms, 1 to 4 heteroatoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and a fused non-aromatic heterocyclic group. Examples of the fused non-aromatic heterocyclic group include a group derived from a fused ring wherein a ring corresponding to such 4- to 7-membered monocyclic non-aromatic heterocyclic group, and 1 or 2 rings selected from a 5- or 6-membered heterocycle containing 1 or 2 nitrogen atoms, a 5-membered heterocycle containing one sulfur atom and a benzene ring and the like are fused, and the like.

[0307]

Preferable examples of the non-aromatic heterocyclic group include

monocyclic non-aromatic heterocyclic groups such as oxetanyl (e.g., 2-oxetanyl, 3-oxetanyl), pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl), piperidinyl (e.g., piperidino, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), morpholinyl (e.g., morpholino), thiomorpholinyl (e.g., thiomorpholino), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl, 3-piperazinyl), hexamethyleniminyl (e.g., hexamethylenimin-1-yl), oxazolidinyl (e.g., oxazolidin-2-yl), thiazolidinyl (e.g., thiazolidin-2-yl), imidazolidinyl (e.g., imidazolidin-2-yl, imidazolidin-3-yl), oxazolinyl (e.g., oxazolin-2-yl), thiazolinyl (e.g., thiazolin-2-yl), imidazolinyl (e.g., imidazolin-2-yl, imidazolin-3-yl), dioxolyl (e.g., 1,3-dioxol-4-yl), dioxolanyl (e.g., 1,3-dioxolan-4-yl), dihydrooxadiazolyl (e.g., 4,5-dihydro-1,2,4-oxadiazol-3-yl), 2-thioxo-1,3-oxazolidin-5-yl, pyranyl (e.g., 4-pyranyl), tetrahydropyranyl (e.g., 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl), thiopyranyl (e.g., 4-thiopyranyl), tetrahydrothiopyranyl (e.g., 2-tetrahydrothiopyranyl, 3-tetrahydrothiopyranyl, 4-tetrahydrothiopyranyl), 1-oxidotetrahydrothiopyranyl (e.g., 1-

oxidotetrahydrothiopyran-4-yl), 1,1-dioxidotetrahydrothiopyranyl (e.g., 1,1-dioxidotetrahydrothiopyran-4-yl), tetrahydrofuryl (e.g., tetrahydrofuran-3-yl, tetrahydrofuran-2-yl), pyrazolidinyl (e.g., pyrazolidin-1-yl, pyrazolidin-3-yl), pyrazolinyl (e.g., pyrazolin-1-yl), tetrahydropyrimidinyl (e.g., tetrahydropyrimidin-1-yl), dihydrotriazolyl (e.g., 2,3-dihydro-1H-1,2,3-triazol-1-yl), tetrahydrotriazolyl (e.g., 2,3,4,5-tetrahydro-1H-1,2,3-triazol-1-yl) and the like;
fused non-aromatic heterocyclic groups such as dihydroindolyl (e.g., 2,3-dihydro-1H-indol-1-yl), dihydroisoindolyl (e.g., 1,3-dihydro-2H-isoindol-2-yl), dihydrobenzofuranyl (e.g., 2,3-dihydro-1-benzofuran-5-yl), dihydrobenzodioxinyl (e.g., 2,3-dihydro-1,4-benzodioxinyl), dihydrobenzodioxepinyl (e.g., 3,4-dihydro-2H-1,5-benzodioxepinyl), tetrahydrobenzofuranyl (e.g., 4,5,6,7-tetrahydro-1-benzofuran-3-yl), chromenyl (e.g., 4H-chromen-2-yl, 2H-chromen-3-yl), dihydroquinolinyl (e.g., 1,2-dihydroquinolin-4-yl), tetrahydroquinolinyl (e.g., 1,2,3,4-tetrahydroquinolin-4-yl), dihydroisoquinolinyl (e.g., 1,2-dihydroisoquinolin-4-yl), tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydroisoquinolin-4-yl), dihydrophthalazinyl (e.g., 1,4-dihydrophthalazin-4-yl) and the like;
and the like.

[0308]

The "heterocyclic group" of the above-mentioned "optionally substituted heterocyclic group" may have one or more (preferably 1 to 5, more preferably 1 to 3) substituents at the substitutable positions. Examples of such substituent include substituents selected from the below-mentioned substituent group V. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

[0309]

Examples of the above-mentioned "optionally substituted

heterocyclyl-C_{1-4} alkyl" include a group wherein C_{1-4} alkyl (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy) is substituted by the above-mentioned "optionally substituted heterocyclic group".

[0310]

Examples of the above-mentioned "optionally substituted heterocyclyl-carbonyl" include a group wherein the above-mentioned "optionally substituted heterocyclic group" is bonded to carbonyl.

[0311]

Examples of the above-mentioned "optionally substituted heterocyclyl-C_{1-4} alkyl-carbonyl" include a group wherein the above-mentioned "optionally substituted heterocyclyl-C_{1-4} alkyl" is bonded to carbonyl.

[0312]

Of the "optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom" for $R^{1''}$, examples of the "optionally substituted group bonded via a nitrogen atom" include

(i) amino,

(ii) amino mono-substituted by the above-mentioned "optionally substituted group bonded via a carbon atom", and

(iii) amino di-substituted by the above-mentioned "optionally substituted group bonded via a carbon atom" and C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, propyl etc.).

[0313]

Of the "optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom" for $R^{1''}$, examples of the "optionally substituted group bonded via an oxygen atom" include hydroxy optionally substituted by the above-mentioned "optionally substituted group bonded via a carbon atom".

[0314]

As $R^{1''}$, a hydrogen atom, a halogen atom or cyano is preferable, and a hydrogen atom or a halogen atom

(particularly, a chlorine atom) is particularly preferable.

[0315]

$R^{2''}$ is a hydrogen atom, or an optionally substituted group bonded via a carbon atom or a sulfur atom.

[0316]

Of the "optionally substituted group bonded via a carbon atom or a sulfur atom" for $R^{2''}$, examples of the "optionally substituted group bonded via a carbon atom" include those similar to the "optionally substituted group bonded via a carbon atom" for $R^{1''}$.

[0317]

Of the "optionally substituted group bonded via a carbon atom or a sulfur atom" for $R^{2''}$, examples of the "optionally substituted group bonded via a sulfur atom" include mercapto optionally substituted by the above-mentioned "optionally substituted group bonded via a carbon atom" wherein the sulfur atom may be oxidized.

[0318]

As R^2, a hydrogen atom or optionally substituted alkyl is preferable. Of these,

(1) a hydrogen atom, or

(2) C_{1-6} alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of

(a) C_{3-6} cycloalkyl,

(b) $-O-(CH_2)_n-OH$,

(c) $-NR^{5''}-(CH_2)_n-OH$,

(d) $-NR^{5''}-CO-$ (C_{1-4} alkyl optionally substituted by 1 to 4 substituents selected from hydroxy, halogen atom, cyano, C_{1-4} alkoxy, amino and di-C_{1-4} alkylamino),

(e) $-NR^{5''}-CO-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(f) $-NR^{5''}-CO-$ (5- or 6-membered heterocycle optionally substituted by 1 or 2 C_{1-4} alkyl),

(g) $-NR^{5''}-CO-(CH_2)_n-$ (6-membered heterocycle optionally substituted by C_{1-4} alkyl),

(h) $-NR^{5''}-CO-$ (C_{3-6} cycloalkyl optionally substituted by

substituent(s) selected from hydroxy and cyano),
(i) $-NR^{5''}-CO-$ (C_{6-10} aryl optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 halogen atoms),
(j) $-NR^{5''}-CO-NR^{5'''}-C_{3-6}$ cycloalkyl,
(k) $-NR^{5''}-SO_2-C_{1-4}$ alkyl,
(l) C_{1-4} alkyl-carbonyl,
(m) (5- or 6-membered heterocycle optionally substituted by 1 or 2 substituents selected from hydroxy and amino)-carbonyl,
(n) hydroxy,
(o) a halogen atom, and
(p) 3- to 6 -membered cyclic amino optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl and oxo,
wherein n is an integer of 1 to 4, $R^{5''}$ and $R^{5'''}$ are each a hydrogen atom or C_{1-4} alkyl, $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl, is preferable,
and particularly, methyl or ethyl substituted by hydroxy is preferable.

[0319]

$R^{3''}$ is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group.

[0320]

Examples of the "aliphatic hydrocarbon group" of the "an optionally substituted aliphatic hydrocarbon group" for $R^{3''}$ include those similar to the "optionally substituted C_{1-8} alkyl", "optionally substituted C_{2-8} alkenyl", "optionally substituted C_{2-8} alkynyl" and "optionally substituted C_{3-8} cycloalkyl" exemplified as the "optionally substituted group bonded via a carbon atom" for $R^{1''}$.

[0321]

As $R^{3''}$, a hydrogen atom is preferable.

[0322]

Ring A" is an optionally substituted benzene ring.

The "benzene ring" of the "optionally substituted benzene ring" for ring A" is optionally substituted by 1 to 5 substituents selected from the group consisting of

(1) C_{3-10} cycloalkyl (e.g., cyclopropyl, cyclohexyl) optionally substituted by 1 to 3 substituents selected from the group consisting of

(a) halogen;

(b) hydroxy;

(c) carboxyl;

(d) sulfo;

(e) cyano;

(f) azido;

(g) nitro;

(h) nitroso;

(i) optionally halogenated C_{1-4} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl);

(j) optionally halogenated C_{2-4} alkenyl (e.g., ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl);

(k) optionally halogenated C_{2-4} alkynyl (e.g., ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl);

(l) C_{3-7} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl);

(m) C_{6-14} aryl (e.g., phenyl, naphthyl, anthryl, phenanthryl, acenaphthyl, biphenylyl);

(n) C_{7-16} aralkyl (e.g., benzyl, phenethyl, phenylpropyl, naphthylmethyl, biphenylylmethyl);

(o) formyl;

(p) optionally halogenated C_{1-6} alkyl-carbonyl (e.g., acetyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, butylcarbonyl, isobutylcarbonyl, sec-butylcarbonyl, tert-butylcarbonyl);

(q) optionally halogenated C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl);

(r) optionally halogenated C_{1-6} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, propylsulfonyl,

isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, sec-butylsulfonyl, tert-butylsulfonyl);

(s) carbamoyl;

(t) carbamoyl mono- or di-substituted by optionally halogenated C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl);

(u) mono- or di-C_{6-14} aryl-carbamoyl (e.g., phenylcarbamoyl, naphthylcarbamoyl, anthrylcarbamoyl, phenanthrylcarbamoyl, acenaphthylcarbamoyl, biphenylylcarbamoyl);

(v) thiocarbamoyl optionally mono- or di-substituted by optionally halogenated C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl);

(w) ureido optionally mono- or di-substituted by optionally halogenated C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl);

(x) mono- or di-C_{6-14} aryl-ureido (e.g., phenylureido, naphthylureido, anthrylureido, phenanthrylureido, acenaphthylureido, biphenylylureido);

(y) sulfamoyl optionally mono- or di-substituted by optionally halogenated C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl);

(z) optionally halogenated C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy);

(aa) optionally halogenated C_{2-6} alkenyloxy (e.g., ethenyloxy, 1-propenyloxy, 2-propenyloxy, 2-methyl-1-propenyloxy, 1-butenyloxy, 2-butenyloxy, 3-butenyloxy);

(bb) C_{3-10} cycloalkyloxy (e.g., cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy);

(cc) C_{7-13} aralkyloxy (e.g., benzyloxy, phenethyloxy, phenylpropyloxy, naphthylmethyloxy, biphenylylmethyloxy);

(dd) C_{6-14} aryloxy (e.g., phenyloxy, naphthyloxy, anthryloxy, phenanthryloxy, acenaphthyloxy, biphenylyloxy);

(ee) C_{1-6} alkyl-carbonyloxy (e.g., acetyloxy, ethylcarbonyloxy, propylcarbonyloxy, isopropylcarbonyloxy,

butylcarbonyloxy, isobutylcarbonyloxy, sec-butylcarbonyloxy, tert-butylcarbonyloxy);

(ff) C_{3-10} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl)-C_{1-6} alkyloxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy);

(gg) C_{1-6} alkylsulfonyloxy (e.g., methylsulfonyloxy, ethylsulfonyloxy, propylsulfonyloxy, isopropylsulfonyloxy, butylsulfonyloxy, isobutylsulfonyloxy, sec-butylsulfonyloxy, tert-butylsulfonyloxy);

(hh) mercapto;

(ii) optionally halogenated C_{1-6} alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio);

(jj) C_{7-13} aralkylthio (e.g., benzylthio, phenethylthio, phenylpropylthio, naphthylmethylthio, biphenylylmethylthio);

(kk) C_{6-14} arylthio (e.g., phenylthio, naphthylthio, anthrylthio, phenanthrylthio, acenaphthylthio, biphenylylthio);

(ll) C_{1-6} alkylsulfinyl (e.g., methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, isobutylsulfinyl, sec-butylsulfinyl, tert-butylsulfinyl);

(mm) oxo;

(nn) C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, propylenedioxy); and

(oo) hydroxyimino optionally substituted by C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl); (hereinafter sometimes to be referred to as substituent group A),

(2) C_{6-14} aryl (e.g., phenyl, naphthyl) optionally substituted by 1 to 3 substituents selected from substituent group A;

(3) a heterocyclic group (the heterocyclic group is similar to the "heterocyclic group" of the "optionally substituted heterocyclic group" exemplified as the "optionally substituted

group bonded via a carbon atom" for $R^{1''}$) optionally substituted by 1 to 3 substituents selected from substituent group A;

(4) amino optionally substituted by 1 or 2 substituents selected from the group consisting of

(a) C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl) optionally substituted by substituent(s) selected from the group consisting of halogen, hydroxy, C_{3-7} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl), C_{1-6} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, sec-butylsulfonyl, tert-butylsulfonyl) and C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy);

(b) optionally halogenated C_{2-4} alkenyl (e.g., ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl);

(c) optionally halogenated C_{2-4} alkynyl (e.g., ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl);

(d) C_{3-7} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl);

(e) C_{6-14} aryl (e.g., phenyl, naphthyl, anthryl, phenanthryl, acenaphthyl, biphenylyl);

(f) C_{7-16} aralkyl (e.g., benzyl, phenethyl, phenylpropyl, naphthylmethyl, biphenylylmethyl);

(g) a 4- to 7-membered (preferably 5- or 6-membered) heterocyclic group (e.g., a non-aromatic heterocyclic group such as morpholinyl etc.) containing, as a ring-constituting atom besides carbon atoms, 1 to 4 heteroatoms selected from an oxygen atom, a sulfur atom and a nitrogen atom;

(h) formyl;

(i) C_{1-6} alkyl-carbonyl (e.g., methylcarbonyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, butylcarbonyl,

isobutylcarbonyl, sec-butylcarbonyl, tert-butylcarbonyl) optionally substituted by substituent(s) selected from the group consisting of halogen, hydroxy, C_{3-7} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl), C_{1-6} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, sec-butylsulfonyl, tert-butylsulfonyl) and C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy);

(j) C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl);

(k) C_{6-14} aryl-carbonyl (e.g., benzoyl);

(l) C_{7-13} aralkyl-carbonyl (e.g., benzylcarbonyl, phenethylcarbonyl);

(m) C_{3-7} cycloalkyl-carbonyl (e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, cycloheptylcarbonyl);

(o) C_{1-6} alkyl-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl);

(p) C_{6-14} aryl-carbamoyl (e.g., phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl);

(q) C_{7-13} aralkyl-carbamoyl (e.g., benzylcarbamoyl);

(r) C_{1-6} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, isopropylsulfonyl);

(s) C_{6-14} arylsulfonyl (e.g., benzenesulfonyl, toluenesulfonyl, 1-naphthalenesulfonyl, 2-naphthalenesulfonyl); and

(t) C_{7-13} aralkylsulfonyl (e.g., benzylsulfonyl) (hereinafter sometimes to be referred to as substituent group B);

(5) amidino;

(6) optionally formylated or halogenated C_{1-6} alkyl-carbonyl (e.g., methylcarbonyl, ethylcarbonyl, propylcarbonyl,

isopropylcarbonyl, butylcarbonyl, isobutylcarbonyl, sec-butylcarbonyl, tert-butylcarbonyl);

(7) optionally halogenated C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl);

(8) optionally halogenated C_{1-6} alkylsulfonyl (e.g., methylsulfonyl);

(9) carbamoyl optionally substituted by 1 or 2 substituents selected from substituent group B;

(10) thiocarbamoyl optionally mono- or di-substituted by optionally halogenated C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl);

(11) ureido optionally substituted by 1 or 2 substituents selected from substituent group B;

(12) sulfamoyl optionally substituted by 1 or 2 substituents selected from substituent group B;

(13) carboxyl;

(14) hydroxy;

(15) C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy) optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, carboxyl, C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy) and C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl);

(16) optionally halogenated C_{2-6} alkenyloxy (e.g., ethenyloxy);

(17) C_{3-10} cycloalkyloxy (e.g., cyclohexyloxy);

(18) C_{7-13} aralkyloxy (e.g., benzyloxy);

(19) C_{6-14} aryloxy (e.g., phenyloxy, naphthyloxy);

(20) C_{1-6} alkyl-carbonyloxy (e.g., acetyloxy, tert-butylcarbonyloxy);

(21) mercapto;

(22) optionally halogenated C_{1-6} alkylthio (e.g., methylthio, ethylthio);

(23) C_{7-13} aralkylthio (e.g., benzylthio);

(24) C_{6-14} arylthio (e.g., phenylthio, naphthylthio);

(25) sulfo;

(26) cyano;

(27) azido;

(28) nitro;

(29) nitroso;

(30) a halogen atom;

(31) C_{1-6} alkylsulfinyl (e.g., methylsulfinyl);

(32) oxo;

(33) C_{3-10} cycloalkyl-C_{1-6} alkyloxy (e.g., cyclopropylmethyloxy);

(34) C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy);

(35) hydroxyimino optionally substituted by C_{1-6} alkyl;

(36) C_{1-10} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl) optionally substituted by 1 to 3 substituents selected from the above-mentioned (1) - (35);

(37) C_{2-10} alkenyl (e.g., ethenyl, 1-propenyl) optionally substituted by 1 to 3 substituents selected from the above-mentioned (1) - (35), and

(38) C_{7-13} aralkyl (e.g., benzyl) optionally substituted by 1 to 3 substituents selected from the above-mentioned (1) - (35)

(hereinafter sometimes to be referred to as substituent group V). When the number of the substituents is not less than 2, the respective substituents may be the same or different.

[0323]

As ring A", a benzene ring optionally substituted by 1 or 2 substituents selected from the group consisting of (1) a halogen atom and (2) C_{1-4} alkyl is preferable. Particularly, a benzene ring optionally substituted by 1 or 2 substituents selected from the group consisting of a halogen atom and methyl is preferable. Especially, a benzene ring optionally substituted by one substituent selected from the group

consisting of a halogen atom and methyl is preferable.

[0324]

Ring B″ is

(i) an optionally substituted fused ring, or

(ii) a pyridine ring having optionally substituted carbamoyl (said pyridine ring is optionally further substituted).

[0325]

The "optionally substituted fused ring" for ring B″ is, for example, an "optionally substituted fused homocyclic ring" or an "optionally substituted fused heterocycle".

The "fused homocyclic ring" of the "optionally substituted fused homocyclic ring" is, for example, a ring wherein two or more, the same or different rings selected from benzene, C_{3-8} cycloalkane (e.g., cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane), C_{3-8} cycloalkene (e.g., cyclopropene, cyclobutene, cyclopentene, cyclohexene, cycloheptene, cyclooctene), C_{4-8} cycloalkadiene (e.g., cyclobutadiene, cyclopentadiene, cyclohexadiene, cycloheptadiene, cyclooctadiene), C_{7-8} cycloalkatriene (e.g., cycloheptatriene, cyclooctatriene) and cyclooctatetraene are fused. Specifically, naphthalene, dihydronaphthalene, tetrahydronaphthalene, hexahydronaphthalene, decahydronaphthalene, pentalene, indene, indane, azulene, heptalene and the like can be mentioned.

The "fused heterocycle" of the "optionally substituted fused heterocycle" is, for example,

a fused aromatic heterocycle such as quinoline, isoquinoline, quinazoline, quinoxaline, benzofuran, benzothiophene, benzooxazole, benzoisoxazole, benzothiazole, benzoimidazole, benzotriazole, indole, indazole, pyrrolopyridine, pyrrolopyrimidine, pyrrolopyrazine, imidazopyridine, imidazopyrazine, imidazopyridazine, pyrazolopyridine, pyrazolothiophene, pyrazolotriazine, triazolopyridine and the like; or

a fused non-aromatic heterocycle such as dihydroindole,

dihydroisoindole, dihydrobenzofuran, dihydrobenzothiophene, dihydrobenzodioxine, dihydrobenzodioxepine, tetrahydrobenzofuran, tetrahydrobenzothiophene, chromene, dihydroquinoline, tetrahydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, dihydrophthalazine, benzooxazoline, benzisoxazoline, benzothiazoline, benzimidazoline, benzotriazoline, indazoline, dihydropyrrolopyridine and the like.

[0326]

The "fused ring" of the "optionally substituted fused ring" for ring B" optionally have one or more (preferably 1 to 5, more preferably 1 to 3) substituents at substitutable positions. Examples of the substituent include substituents selected from substituent group V and C_{2-4} alkylene (e.g., ethylene, propylene, trimethylene, tetramethylene). The C_{2-4} alkylene may be bonded to a single carbon atom of ring B" to form a spiro ring. When the number of substituents is two or more, the respective substituents may be the same or different.

[0327]

The "optionally substituted carbamoyl" of the "pyridine ring having optionally substituted carbamoyl" for ring B" is, for example, carbamoyl optionally mono- or di-substituted by a group similar to the "optionally substituted group bonded via carbon atom" exemplified for $R^{1"}$.

The "pyridine ring having optionally substituted carbamoyl" for ring B" is optionally further substituted, and the substituent that is optionally further present is, for example, a substituent selected from substituent group V.

[0328]

As ring B",

(1) a fused ring optionally substituted by substituent selected from the group consisting of

(a) halogen atom,

(b) cyano,

(c) C_{1-6} alkyl optionally substituted by halogen atom or C_{3-6}

cycloalkyl,

(d) oxo,

(e) C_{2-4} alkylene,

(f) hydroxy,

(g) carbamoyl,

(h) C_{1-6} alkyl-carbamoyl, and

(i) C_{1-6} alkoxy-carbonyl, or

(2) a pyridine ring having carbamoyl optionally substituted by C_{1-6} alkyl (said pyridine ring is optionally further substituted by C_{1-6} alkyl)

is preferable.

[0329]

Particularly,

(1) a fused homocyclic ring (e.g., indane, naphthalene) optionally having, as substituent, 1 or 2 substituents selected from the group consisting of (a) C_{1-6} alkyl optionally substituted by halogen atom, (b) hydroxy and (c) oxo;

(2) a fused heterocycle (e.g., quinoline, isoquinoline, quinazoline, quinoxaline, benzooxazoline, benzisoxazoline, benzothiazoline, benzimidazoline, benzotriazoline, indole, indazole, pyrrolopyridine, dihydropyrrolopyridine, benzoxazole, benzimidazole, benzothiazole, benzisoxazole, benzisothiazole, pyrrolopyrimidine, imidazopyridazine, indazoline, pyrrolopyrazine, imidazopyridine, imidazopyrazine, pyrazolopyridine, pyrazolothiophene, pyrazolotriazine, dihydroindole, dihydroisoindole, dihydroquinoline, tetrahydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, dihydrophthalazine, dihydrobenzoxazole, benzothiophene, benzofuran, dihydrobenzothiophene, dihydrobenzofuran and the like) optionally having, as substituent, 1 to 4 substituents selected from the group consisting of (a) halogen atom, (b) cyano, (c) C_{1-6} alkyl optionally substituted by halogen atom or C_{3-6} cycloalkyl, (d) oxo, (e) C_{2-4} alkylene, (f) carbamoyl, (g) C_{1-6} alkyl-carbamoyl, and (h) C_{1-6} alkoxy-carbonyl; or

(3) a pyridine ring having carbamoyl optionally substituted by C_{1-8} alkyl (said pyridine ring is optionally further substituted by C_{1-6} alkyl);

is preferable.

[0330]

Especially,

(1) indole optionally having one C_{1-4} alkyl;

(2) pyrrolopyrimidine optionally having one C_{1-4} alkyl;

(3) imidazopyridine;

(4) dihydroindole optionally having 1 or 2 substituents selected from the group consisting of

(a) C_{1-4} alkyl optionally substituted by C_{3-6} cycloalkyl, (b) halogen atom, (c) C_{2-4} alkylene and (d) oxo;

(5) dihydroisoindole optionally having 1 to 4 substituents selected from the group consisting of

(a) C_{1-4} alkyl, (b) halogen atom and (c) oxo;

(6) dihydrobenzoxazole optionally having 1 or 2 substituents selected from the group consisting of C_{1-4} alkyl and oxo;

(7) pyrrolopyridine;

(8) indane optionally having 1 or 2 substituents selected from

(a) C_{1-6} alkyl optionally substituted by 1 to 3 halogen atoms,

(b) hydroxy and (c) oxo;

(9) benzothiophene;

(10) indazole optionally having one substituent selected from the group consisting of halogen atom and C_{1-4} alkyl;

(11) dihydrobenzofuran;

(12) quinoline optionally having one substituent selected from the group consisting of

(a) halogen atom and (b) C_{1-6} alkyl optionally substituted by 1 to 3 halogen atoms;

(13) benzooxazole;

(14) benzofuran optionally having one substituent selected from the group consisting of

(a) cyano and (b) carbamoyl;

(15) benzoisoxazole optionally having one C_{1-4} alkyl;

(16) pyrazolopyridine optionally having one substituent selected from the group consisting of
(a) C_{1-6} alkoxy-carbonyl and (b) C_{1-6} alkyl-carbamoyl;
(17) benzoimidazole optionally having 1 or 2 C_{1-4} alkyl;
(18) triazolopyridine;
(19) naphthalene; or
(20) pyridine substituted by C_{1-8} alkyl-carbamoyl and optionally further substituted by C_{1-6} alkyl;
is preferable.

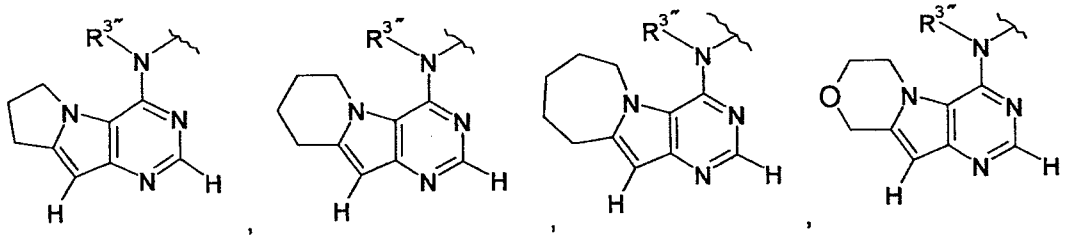
[0331]

$R^{1''}$ and $R^{2''}$ are optionally bonded to each other to form an optionally substituted ring structure. Examples of the "ring structure" include a saturated or unsaturated (preferably saturated) 4- to 8-membered (preferably 5- to 7-membered) heterocycle.

[0332]

Examples of the "ring structure" of the "optionally substituted ring structure" formed by $R^{1''}$ and $R^{2''}$ bonded to each other include

[0333]



[0334]

wherein each symbol is as defined above,
and the like.

[0335]

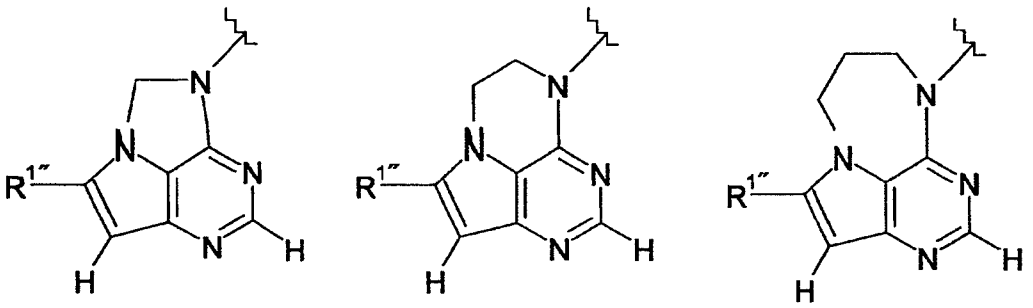
$R^{2''}$ and $R^{3''}$ are optionally bonded to each other to form an optionally substituted ring structure. Examples of the "ring structure" include a saturated or unsaturated (preferably saturated) 4- to 8-membered (preferably 5- to 7-membered)

heterocycle.

[0336]

Examples of the "ring structure" of the "optionally substituted ring structure" formed by $R^{2''}$ and $R^{3''}$ bonded to each other include

[0337]



[0338]

wherein each symbol is as defined above,

and the like.

[0339]

The "ring structure" of the "optionally substituted ring structure" formed by $R^{1''}$ and $R^{2''}$, or $R^{2''}$ and $R^{3''}$ bonded respectively, optionally has 1 to 5 (preferably 1 to 3, more preferably 1 or 2), the same or different substituents at any substitutable positions. Examples of the substituent include substituents selected from substituent group V. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

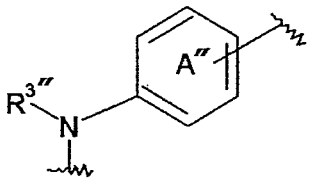
[0340]

Examples of the "ring structure" of the "optionally substituted ring structure" formed by $R^{3''}$ bonded to the carbon atom on the adjacent benzene ring (ring A") include a saturated or unsaturated (preferably saturated) 4- to 8-membered (preferably 5- or 6-membered) nitrogen-containing heterocycle.

[0341]

Specifically, the moiety of

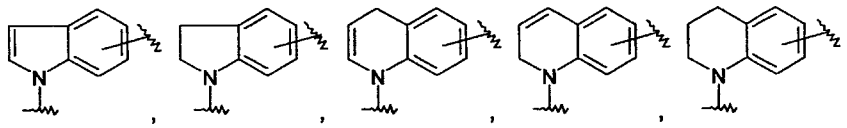
[0342]



[0343]

wherein each symbol is as defined above, is, for example,

[0344]



[0345]

[0346]

The "ring structure" optionally has 1 to 5 (preferably 1 to 3, more preferably 1 or 2), the same or different substituents at any substitutable positions. Examples of the substituent include substituents selected from substituent group V. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

[0347]

Preferable compounds of compound (I") are as follows.

[Compound A]

Compound (I") wherein

$R^{1"}$ is a hydrogen atom, a halogen atom or cyano;

$R^{2"}$ is a hydrogen atom or optionally substituted alkyl;

$R^{3"}$ is a hydrogen atom;

ring A" is a benzene ring optionally substituted by 1 or 2 substituents selected from the group consisting of (1) a halogen atom and (2) C_{1-4} alkyl; and

ring B" is

(1) a fused ring optionally substituted by substituent selected from the group consisting of

(a) a halogen atom,

(b) cyano,

(c) C_{1-6} alkyl optionally substituted by halogen atom or C_{3-6} cycloalkyl,

(d) oxo,

(e) C_{2-4} alkylene,

(f) hydroxy,

(g) carbamoyl,

(h) C_{1-6} alkyl-carbamoyl, and

(i) C_{1-6} alkoxy-carbonyl, or

(2) a pyridine ring having carbamoyl optionally substituted by C_{1-6} alkyl (said pyridine ring is optionally further substituted by C_{1-6} alkyl).

[0348]

[Compound B]

Compound (I'') wherein

$R^{1''}$ is a hydrogen atom, a halogen atom or cyano;

$R^{2''}$ is

(1) a hydrogen atom, or

(2) C_{1-6} alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of

(a) C_{3-6} cycloalkyl,

(b) $-O-(CH_2)_n-OH$,

(c) $-NR^{5''}-(CH_2)_n-OH$,

(d) $-NR^{5''}-CO-$ (C_{1-4} alkyl optionally substituted 1 to 4 substituent selected from hydroxy, halogen atom, cyano, C_{1-4} alkoxy, amino and di-C_{1-4} alkylamino),

(e) $-NR^{5''}-CO-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(f) $-NR^{5''}-CO-$ (5- or 6-membered heterocycle optionally substituted by 1 or 2 C_{1-4} alkyl),

(g) $-NR^{5''}-CO-(CH_2)_n-$ (6-membered heterocycle optionally substituted by C_{1-4} alkyl),

(h) $-NR^{5''}-CO-$ (C_{3-6} cycloalkyl optionally substituted by substituent(s) selected from hydroxy and cyano),

(i) $-NR^{5''}-CO-$ (C_{6-10} aryl optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 halogen atoms),

(j) $-NR^{5''}-CO-NR^{5'''}-C_{3-6}$ cycloalkyl,

(k) $-NR^{5''}-SO_2-C_{1-4}$ alkyl,

(l) C_{1-4} alkyl-carbonyl,

(m) (5- or 6-membered heterocycle optionally substituted by 1 or 2 substituents selected from hydroxy and amino)-carbonyl,

(n) hydroxy,

(o) halogen atom, and

(p) 3- to 6-membered cyclic amino optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl and oxo,

wherein n is an integer of 1 to 4, $R^{5''}$ and $R^{5'''}$ are each a hydrogen atom or C_{1-4} alkyl, $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl);

$R^{3''}$ is a hydrogen atom;

ring A'' is a benzene ring optionally substituted by 1 or 2 substituents selected from the group consisting of (1) a halogen atom and (2) C_{1-4} alkyl; and

ring B'' is

(1) a fused homocyclic ring optionally having, as substituent, 1 or 2 substituents selected from the group consisting of (a) C_{1-6} alkyl optionally substituted by halogen atom, (b) hydroxy and (c) oxo;

(2) fused heterocycle optionally having, as substituent, 1 to 4 substituents selected from the group consisting of (a) a halogen atom, (b) cyano, (c) C_{1-6} alkyl optionally substituted by halogen atom or C_{3-6} cycloalkyl, (d) oxo, (e) C_{2-4} alkylene, (f) carbamoyl, (g) C_{1-6} alkyl-carbamoyl, and (h) C_{1-6} alkoxy-carbonyl; or

(3) a pyridine ring having carbamoyl optionally substituted by C_{1-8} alkyl (said pyridine ring is optionally further substituted by C_{1-6} alkyl).

[0349]

[Compound C]

Compound (I'') wherein

$R^{1''}$ is a hydrogen atom, a halogen atom or cyano;

$R^{2''}$ is

(1) a hydrogen atom, or

(2) C_{1-6} alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of

(a) C_{3-6} cycloalkyl,

(b) $-O-(CH_2)_n-OH$,

(c) $-NR^{5''}-(CH_2)_n-OH$,

(d) $-NR^{5''}-CO-$ (C_{1-4} alkyl optionally substituted by 1 to 4 substituent selected from hydroxy, halogen atom, cyano, C_{1-4} alkoxy, amino and di-C_{1-4} alkylamino),

(e) $-NR^{5''}-CO-(CH_2)_n-SO_2-C_{1-4}$ alkyl,

(f) $-NR^{5''}-CO-$ (5- or 6-membered heterocycle optionally substituted by 1 or 2 C_{1-4} alkyl),

(g) $-NR^{5''}-CO-(CH_2)_n-$ (6-membered heterocycle optionally substituted by C_{1-4} alkyl),

(h) $-NR^{5''}-CO-$ (C_{3-6} cycloalkyl optionally substituted by substituent(s) selected from hydroxy and cyano),

(i) $-NR^{5''}-CO-$ (C_{6-10} aryl optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 halogen atoms),

(j) $-NR^{5''}-CO-NR^{5'''}-C_{3-6}$ cycloalkyl,

(k) $-NR^{5''}-SO_2-C_{1-4}$ alkyl,

(l) C_{1-4} alkyl-carbonyl,

(m) (5- or 6-membered heterocycle optionally substituted by 1 or 2 substituents selected from hydroxy and amino)-carbonyl,

(n) hydroxy,

(o) halogen atom, and

(p) 3- to 6-membered cyclic amino optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl and oxo,

wherein n is an integer of 1 to 4, R^5 and $R^{5'}$ are each a hydrogen atom or C_{1-4} alkyl, $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl;

$R^{3''}$ is a hydrogen atom;

ring A'' is a benzene ring optionally substituted by 1 or 2 substituents selected from the group consisting of (1) a halogen atom and (2) C_{1-4} alkyl; and

ring B'' is

(1) indole optionally having one C_{1-4} alkyl;

(2) pyrrolopyrimidine optionally having one C_{1-4} alkyl;

(3) imidazopyridine;

(4) dihydroindole optionally having 1 or 2 substituents selected from the group consisting of (a) C_{1-4} alkyl optionally substituted by C_{3-6} cycloalkyl, (b) a halogen atom, (c) C_{2-4} alkylene and (d) oxo;

(5) dihydroisoindole optionally having 1 to 4 substituents selected from the group consisting of (a) C_{1-4} alkyl, (b) a halogen atom and (c) oxo;

(6) dihydrobenzoxazole optionally having 1 or 2 substituents selected from the group consisting of C_{1-4} alkyl and oxo;

(7) pyrrolopyridine;

(8) indane optionally having 1 or 2 substituents selected from (a) C_{1-6} alkyl optionally substituted by 1 to 3 halogen atoms, (b) hydroxy and (c) oxo;

(9) benzothiophene;

(10) indazole optionally having one substituent selected from the group consisting of a halogen atom and C_{1-4} alkyl;

(11) dihydrobenzofuran;

(12) quinoline optionally having one substituent selected from the group consisting of (a) a halogen atom and (b) C_{1-6} alkyl optionally substituted by 1 to 3 halogen atoms;

(13) benzooxazole;

(14) benzofuran optionally having one substituent selected from the group consisting of (a) cyano and (b) carbamoyl;

(15) benzoisoxazole optionally having one C_{1-4} alkyl;

(16) pyrazolopyridine optionally having one substituent selected from the group consisting of (a) C_{1-6} alkoxy-carbonyl and (b) C_{1-6} alkyl-carbamoyl;

(17) benzoimidazole optionally having 1 or 2 C_{1-4} alkyl;

(18) triazolopyridine;

(19) naphthalene; or

(20) pyridine substituted by C_{1-8} alkyl-carbamoyl and optionally further substituted by C_{1-6} alkyl.

[0350]

As the salts of the compound (I"), for example, metal salt, ammonium salt, salts with organic base, salts with inorganic acid, salts with organic acid, salts with basic or acidic amino acid and the like can be mentioned.

[0351]

As preferable examples of the metal salt, for example, alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt, barium salt and the like; aluminum salt and the like can be mentioned.

[0352]

As preferable examples of the salts with organic base, for example, salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, tromethamine [tris(hydroxymethyl)methylamine], t-butylamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like can be mentioned.

[0353]

As preferable examples of salts with inorganic acid, for example, salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like can be mentioned.

[0354]

As preferable examples of the salts with organic acid, for example, salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like can be mentioned.

[0355]

As preferable examples of the salts with basic amino acid, for example, salts with arginine, lysine, ornithine and the like can be mentioned.

[0356]

As preferable examples of the salts with acidic amino acid, for example, salts with aspartic acid, glutamic acid and the like can be mentioned.

[0357]

Of these, pharmaceutically acceptable salts are preferable. For example, when a compound contains an acidic functional group, inorganic salts such as alkali metal salts (e.g., sodium salt, potassium salt etc.), alkaline earth metal salts (e.g., calcium salt, magnesium salt, barium salt etc.) and the like, ammonium salt and the like, and when a compound contains a basic functional group, for example, salts with inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like, or salts with organic acid such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like can be mentioned.

[0358]

Among the above-mentioned compounds (I) - (I"), a HER2 inhibitor most preferable for the prophylaxis or treatment of a HER2 inhibitor (trastuzumab and the like)-resistant cancer is N-{2-[4-({3-chloro-4-[3-(trifluoromethyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide (compound A).

[0359]

Compound (I) and a salt thereof can be produced according to the method described in WO2005/118588.

Compound (I') and a salt thereof can be produced according to the method described in WO2007/064045.

Compound (I") and a salt thereof can be produced according to the method described in WO2007/073879.

[0360]

When compound (I) - (I") has isomers such as optical isomer, stereoisomer, positional isomer, rotational isomer and

the like, and any isomers and mixtures are encompassed in the compound (I) - (I"). For example, when compound (I) - (I") has an optical isomer, an optical isomer separated from a racemate is also encompassed in the compound (I) - (I"). These isomers can be obtained as independent products by a synthesis means or a separation means (concentration, solvent extraction, column chromatography, recrystallization and the like) known *per se*.

[0361]

Compounds (I) - (I") may be a crystal, and both a single crystal and crystal mixtures are encompassed in the compound (I) - (I"). Crystals can be produced by crystallization according to crystallization methods known *per se*.

[0362]

Compounds (I) - (I") may be a solvate (e.g., hydrate etc.) or a non-solvate, both of which are encompassed in the compound (I) - (I").

[0363]

A compound labeled with an isotope (e.g., ^{3}H, ^{14}C, ^{35}S, ^{125}I and the like) is also encompassed in the compound (I) - (I").

[0364]

A prodrug of the compound (I) - (I") or a salt thereof (hereinafter referred to as compound (I) - (I")) means a compound which is converted to the compound (I) - (I") with a reaction due to an enzyme, an gastric acid, etc. under the physiological condition in the living body, that is, a compound which is converted to the compound (I) - (I") with oxidation, reduction, hydrolysis, etc. according to an enzyme; a compound which is converted to the compound (I) - (I") by hydrolysis etc. due to gastric acid, etc. A prodrug for compound (I) - (I") may be a compound obtained by subjecting an amino group in compound (I) - (I") to an acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting an amino group in compound (I) - (I") to an

eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation and tert-butylation, etc.); a compound obtained by subjecting a hydroxy group in compound (I) - (I") to an acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting an hydroxy group in compound (I) - (I") to an acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation, dimethylaminomethylcarbonylation, etc.); a compound obtained by subjecting a carboxyl group in compound (I) - (I") to an esterification or amidation (e.g., a compound obtained by subjecting a carboxyl group in compound (I) - (I") to an ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification and methylamidation, etc.) and the like. Any of these compounds can be produced from compound (I) - (I") by a method known *per se*.

[0365]

A prodrug of compound (I) - (I") may also be converted to compound (I) - (I") under physiological conditions, such as those described in IYAKUHIN no KAIHATSU (Development of Pharmaceuticals), Vol. 7, Design of Molecules, p.163-198, Published by HIROKAWA SHOTEN (1990).

[0366]

The "combination drug comprising (1) a HER2 inhibitor and (2) one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a RHO inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor" of the present invention means a concomitant or combination agent of two or more medicaments.

[0367]

The "combination drug comprising (1) a HER2 inhibitor and (2) one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a RHO inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor" of the present invention includes both a single preparation comprising (1) a HER2 inhibitor and (2) one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor, and separate preparations each comprising (1) a HER2 inhibitor or (2) one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor. These are generically abbreviated as the combination drug of the present invention.

The combination drug of the present invention can be formulated into a preparation according to a method similar to that for the aforementioned agent for preventing or treating cancer of the present invention by directly using (1) a HER2 inhibitor and (2) one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor or by mixing them with a pharmaceutically acceptable carrier and the like separately or simultaneously. The daily dose of the combination drug of the present invention varies depending on the severity of the symptom, age, sex, body weight and sensitivity difference of the subject, period and interval of administration, and properties, dosage form and kind of the pharmaceutical composition, kind of effective ingredient, and the like, and is not particularly restricted. The dose of each of (1) a HER2 inhibitor and (2) one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor is any as long as the side effects thereof are not problematic, and is not particularly limited. For oral administration, the dose is generally about 0.005 - 100 mg, preferably about 0.05 - 50 mg, more preferably about 0.2 - 30

mg, per 1 kg of a mammal, which is normally administered in one to 3 portions a day.

For administration of the combination drug of the present invention, (1) a HER2 inhibitor and (2) one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor may be administered simultaneously, or (1) a HER2 inhibitor may be administered earlier and then (2) one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor may be administered, or (1) one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor may be administered earlier and then (2) a HER2 inhibitor may be administered. In administration in a staggered manner, the time difference varies depending on the active ingredient to be administered, dosage form and administration method. For example, when a HER2 inhibitor is to be administered earlier, a method including administering one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor within one min - 3 days, preferably 10 min - 1 day, more preferably 15 min - 1 hr, after administration of the HER2 inhibitor can be employed. When one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor is/are to be administered earlier, a method including administering a HER2 inhibitor within one min - 1 day, preferably 10 min - 6 hr, more preferably 15 min - 1 hr, after administration of one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor can be employed.

In the "combination drug of the present invention

comprising (1) a HER2 inhibitor and (2) one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a RHO inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor", the content of each of the HER2 inhibitor and one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor varies depending on the form of the preparation. It is generally about 0.01 - 90 wt%, preferably about 0.1 - 50 wt%, more preferably about 0.5 - 20 wt%, relative to the whole preparation.

The content of the carrier in the combination drug is generally about 0 - 99.8 wt%, preferably about 10 - 99.8 wt%, more preferably about 10 - 90 wt%, relative to the whole preparation.

In the combination drug of the present invention separately comprising (1) a HER2 inhibitor and (2) one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor, the pharmaceutical composition containing a HER2 inhibitor can be produced and used in the same manner as in the agent for preventing or treating cancer of the present invention.

[0368]

The present invention also provides a method of examining the sensitivity of a HER2-expressing cancer to a HER2 inhibitor, comprising measuring the expression or activation state of one or more selected from cofilin, PAK1, LIMK, RHO, ROCK1 and ROCK2 in a sample collected from an animal having the cancer. The sample is, for example, a cancer tissue. As a control, an animal-derived sample known to be highly sensitive to a HER2 inhibitor can be used. The expression and activation states of cofilin, PAK1, LIMK, Rho, ROCK1 and ROCK2 can be measured by a method similar to the screening method of the present invention mentioned above. By comparison of the

measurement values of test animal and control animal, when the expression or activation state of one or more selected from cofilin, PAK1, LIMK, Rho, ROCK1 and ROCK2 shows a significant increase in the test animal than in the control animal, the test animal can be judged to highly possibly show decreased sensitivity to the HER2 inhibitor.

[0369]

The present invention also provides a method of treating cancer, which comprises using HER2 inhibitor and one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor in combination for an animal judged to highly possibly show decreased sensitivity to a HER2 inhibitor by the above-mentioned examination method. The detail of the combined use of a HER2 inhibitor and one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor is as described above.

[0370]

A HER2 inhibitor comprising compounds (I) - (I") (particularly compound A) (hereinafter sometimes to be referred to as "the HER2 inhibitor of the present invention") or a salt thereof or a prodrug thereof is useful as a therapeutic agent that suppresses growth of a trastuzumab-resistant cancer expressing HER2 and/or EGFR kinase, since it inhibits HER2 kinase and/or EGFR kinase. The HER2 inhibitor of the present invention can be used for the prophylaxis or treatment of a trastuzumab-resistant cancer not only when it is combined with one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor, but also when it is used singly.

[0371]

In particular, of the HER2 inhibitors of the present invention, a trastuzumab-resistant cancer can be prevented or

treated extremely effectively by using N-{2-[4-({3-chloro-4-[3-(trifluoromethyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide (compound A) alone (see the below-mentioned Example 7).

[0372]

Lapatinib can also prevent or treat a trastuzumab-resistant cancer not only when it is combined with one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor, but also when it is used singly, as in the case of the above-mentioned HER2 inhibitor of the present invention (see the below-mentioned Example 8).

[0373]

The HER2 inhibitor of the present invention and lapatinib are useful as medicaments since they show low toxicity (e.g., acute toxicity, chronic toxicity, genetic toxicity, reproductive toxicity, cardiotoxicity, drug interaction, carcinogenicity and the like), high water solubility, and superior stability, in vivo kinetics (absorbability, distribution, metabolism, excretion and the like) and efficacy expression.

[0374]

The HER2 inhibitor of the present invention or Lapatinib can prevent or treat HER2 positive cancers including various cancers (particularly, breast cancer (e.g., invasive ductal carcinoma, ductal cancer in situ, inflammatory breast cancer etc.), prostate cancer (e.g., hormone-dependent prostate cancer, non-hormone dependent prostate cancer etc.), pancreatic cancer (e.g., pancreatic duct cancer etc.), gastric cancer (e.g., papillary adenocarcinoma, mucinous adenocarcinoma, adenosquamous carcinoma etc.), lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, malignant mesothelioma etc.), colon cancer (e.g., gastrointestinal stromal tumor etc.), rectal cancer (e.g., gastrointestinal stromal tumor etc.), colorectal cancer (e.g.,

familial colorectal cancer, hereditary nonpolyposis colorectal cancer, gastrointestinal stromal tumor etc.), small intestinal cancer (e.g., non-Hodgkin lymphoma, gastrointestinal stromal tumor, etc.), esophagus cancer, duodenal cancer, cancer of the tongue, pharyngeal cancer (e.g., nasopharyngeal carcinoma, oropharyngeal cancer, hypopharyngeal cancer etc.), salivary gland cancer, brain tumor (e.g., pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma etc.), schwannoma, liver cancer (e.g., primary liver cancer, extrahepatic bile duct cancer etc.), kidney cancer (e.g., renal cell carcinoma, transitional cell cancers of renal pelvis and ureter etc.), biliary tract cancer, endometrial carcinoma, carcinoma of the uterine cervix, ovary cancer (e.g., ovarian epithelial cancer, extragonadal germ cell tumor, ovarian germ cell tumor, ovarian low malignant potential tumor etc.), urinary bladder cancer, urethral cancer, skin cancer (e.g., ocular melanoma, Merkel cell carcinoma etc.), Hemangioma, malignant lymphoma, malignant melanoma, thyroid cancer (e.g., medullary thyroid carcinoma etc.), parathyroid cancer, nasal cavity cancer, paranasal sinus cancer, bone tumor (e.g., osteosarcoma, Ewing's tumor, uterus sarcoma, soft tissue sarcoma etc.), vascular fibroma, retinoblastoma, penile cancer, testis tumor, solid cancer in childhood (e.g., Wilms' tumor, childhood kidney tumor, etc.), Kaposi's sarcoma, Kaposi's sarcoma related to AIDS, maxillary tumor, fibrous histiocytoma, leiomyosarcoma, rhabdomyosarcoma, leukemia (e.g., acute myelocytic leukemia, acute lymphoblastic leukemia etc.) etc.), and the like. The HER2 inhibitor of the present invention or lapatinib is particularly useful for the prophylaxis or treatment of breast cancer, prostate cancer, gastric cancer, lung cancer, colon cancer, rectal cancer, colorectal cancer, esophagus cancer, pharyngeal cancer, ovary cancer, urinary bladder cancer and the like.

[0375]

The HER2 inhibitor of the present invention or lapatinib

can prevent or treat these cancers even by administration without combination with one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor (namely, as a single agent/alone).

[0376]

The HER2 inhibitor of the present invention or lapatinib can be directly used as it is as a medicament or as a pharmaceutical composition containing a pharmaceutically acceptable carrier known *per se* etc. for a mammal (e.g., human, horse, bovine, dog, cat, rat, mouse, rabbit, swine, monkey etc.). A pharmaceutical composition to be used for administration may contain the HER2 inhibitor of the present invention or lapatinib, and a pharmacologically acceptable carrier, diluent or excipient.

[0377]

The HER2 inhibitor of the present invention or lapatinib can be safely administered orally or parenterally (e.g., topical, rectal, intravenous administrations etc.) as a single agent, or a pharmaceutical composition containing a pharmacologically acceptable carrier according to a conventional method (e.g., a method described in the Japanese Pharmacopoeia etc.), such as tablet (including sugar-coated tablet, film-coated tablet), powder, granule, capsule, liquid, emulsion, suspension, injection, suppository, sustained release preparation, plaster and the like.

[0378]

As a medicament for mammals such as humans, the HER2 inhibitor of the present invention or lapatinib can be generally administered orally in the form of, for example, tablets, capsules (including soft capsules and microcapsules), powders, granules and the like, or parenterally in the form of injections, suppositories, pellets and the like. Examples of the "parenteral administration route" include intravenous, intramuscular, subcutaneous, intra-tissue, intranasal,

intradermal, instillation, intracerebral, intrarectal, intravaginal, intraperitoneal and intratumoral administrations, as well as administration to the vicinity and the like of tumor, or directly to the lesion.

[0379]

As examples of the composition for parenteral administration, injections, suppositories and the like are used; the injections may include dosage forms such as intravenous injections, subcutaneous injections, intracutaneous injections, intramuscular injections, and drip infusion injections. Such an injection can be prepared according to a commonly known method. The injection can be prepared by, for example, dissolving, suspending or emulsifying the above-mentioned HER2 inhibitor of the present invention or lapatinib in a sterile aqueous or oily solution normally used for injections. As examples of aqueous solutions for injection, physiological saline, an isotonic solution containing glucose or other auxiliary agent and the like can be used, which may be used in combination with an appropriate solubilizer, for example, an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a non-ionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)] and the like. As examples of oily solutions, sesame oil, soybean oil and the like can be used, which may be used in combination with solubilizers such as benzyl benzoate, benzyl alcohol. The injectable preparation prepared is preferably filled in an appropriate ampoule. A suppository used for rectal administration may also be prepared by mixing the above-mentioned HER2 inhibitor of the present invention or lapatinib in an ordinary suppository base.

[0380]

As the composition for oral administration, solid or liquid dosage forms, specifically tablets (including sugar-coated tables and film-coated tablets), pills, granules,

powders, capsules (including soft capsules), syrups, emulsions, suspensions and the like can be mentioned. Such a composition is produced by a commonly known method, and may contain a carrier, diluent or filler normally used in the field of pharmaceutical production. As the carrier or filler for tablets, for example, lactose, starch, sucrose, and magnesium stearate are used.

[0381]

The above-described pharmaceutical composition for parenteral or oral administration is conveniently prepared in a medication unit dosage form suitable for the dosage of the active ingredient. As examples of such a medication unit dosage form, tablets, pills, capsules, injections (ampoules), and suppositories can be mentioned.

While the content of the HER2 inhibitor of the present invention or Lapatinib varies depending on the form of the preparation, it is generally about 0.01 - 100 wt%, preferably about 0.1 - 50 wt%, more preferably about 0.5 - 20 wt%, of the whole preparation.

[0382]

The HER2 inhibitor of the present invention or lapatinib can be administered orally or parenterally as they are, or in the form of a solid agent such as powder, fine granules, granules, tablet, capsule and the like or a liquid such as injection and the like by mixing with an appropriate pharmaceutically acceptable carrier, such as excipient (e.g., starch, lactose, sucrose, calcium carbonate, calcium phosphate and the like), binder (e.g., starch, gum arabic, carboxymethylcellulose, hydroxypropylcellulose, crystalline cellulose, alginic acid, gelatin, polyvinylpyrrolidone and the like), lubricant (for example, stearic acid, magnesium stearate, calcium stearate, talc and the like), disintegrant (e.g., calcium carboxymethylcellulose, talc and the like), diluent (e.g., water for injection, saline and the like), additive (stabilizer, preservative, colorant, flavor,

solubilizer, emulsifier, buffer agent, isotonicity agent and the like) as necessary and the like by a conventional method.

The content of the carrier in the preparation is generally about 0 - 99.9 wt%, preferably about 10 - 99.9 wt%, more preferably about 10 - 90 wt%, of the whole preparation.

[0383]

The dose of the HER2 inhibitor of the present invention or Lapatinib varies depending on the kind thereof, level of symptoms, age, sex, body weight and sensitivity difference of the subject of administration, timing of administration, administration route, administration intervals, properties, dosage form and kind of the pharmaceutical composition, and the like. Examples are shown in the following.

[0384]

While the dose of the HER2 inhibitor of the present invention (i.e., compounds (I) - (I")) varies depending on the administration route, symptom and the like, for example, for oral administration to a patient (body weight 40 - 80 kg) with breast cancer or prostate cancer as an anti-cancer agent, the dose is, for example, 0.5 - 300 mg/kg body weight/day, preferably 0.5 - 100 mg/kg body weight/day, more preferably 1 - 50 mg/kg body weight/day, further preferably 1 - 25 mg/kg body weight/day, which can be administered once or in 2 or 3 portions a day.

[0385]

Particularly when compound A is used from among the HER2 inhibitors of the present invention, the dose varies depending on the administration route, symptom and the like, for example, for oral administration to a patient (body weight 40 - 80 kg) with breast cancer or prostate cancer as an anti-cancer agent, the dose is, for example, 0.5 - 300 mg/kg body weight/day, preferably 1 - 250 mg/kg body weight/day, more preferably 10 - 200 mg/kg body weight/day, which can be administered once or in 2 or 3 portions a day.

[0386]

While the dose of lapatinib varies depending on the administration route, symptom and the like, for example, for oral administration to a patient (body weight 40 - 80 kg) with breast cancer or prostate cancer as an anti-cancer agent, the dose is, for example, 1000 - 1500 mg/day, preferably 1200 - 1300 mg/day, generally 1250 mg/day, which can be administered once or in 2 or 3 portions a day. Generally, the amount is administered once a day.

[0387]

In the case of other parenteral administrations and oral administration, a dose based thereon can be administered. When the symptom is particularly severe, the dosage may be increased depending on the symptom.

[0388]

For administration of a sustained-release preparation, the dose of the HER2 inhibitor of the present invention or Lapatinib varies depending on the kind and content thereof, dosage form, duration of sustained drug release, animal as administration subject and administration object. For example, in the case of parenteral administration, about 0.1 to about 100 mg of the HER2 inhibitor of the present invention or Lapatinib only needs to be released from the administered preparation in one week.

[0389]

As long as an unpreferable interaction is not caused by blending the HER2 inhibitor of the present invention or lapatinib, a pharmaceutical composition may contain the HER2 inhibitor of the present invention or Lapatinib along with other active ingredients, for example, the following hormonal therapeutic agent, anti-cancer agent (e.g., chemotherapeutic agent, immunotherapeutic agent, or medicament that inhibits the action of cell growth factor and cell growth factor receptor etc.) and the like.

[0390]

(1) Administration of an effective amount of the HER2

inhibitor of the present invention or lapatinib and (2) a combination of 1 to 3 selected from the group consisting of (i) administering an effective amount of other anticancer agents, (ii) administering an effective amount of hormonal therapeutic agents and (iii) non-drug therapy can prevent and/or treat cancer more effectively. As the non-drug therapy, for example, surgery, radiotherapy, gene therapy, thermotherapy, cryotherapy, laser cauterization and the like are exemplified and two or more of these may be combined.

[0391]

For example, the HER2 inhibitor of the present invention or lapatinib can be administered simultaneously with other hormonal therapeutic agents, anticancer agents (e.g., chemotherapeutic agents, immunotherapeutic agents, or medicaments inhibiting the action of cell growth factors or cell growth factor receptors) (hereafter, these are referred to as a concomitant drug).

[0392]

The HER2 inhibitor of the present invention or Lapatinib as a single agent shows a superior anticancer action on a trastuzumab-resistant cancer. Such effect can be enhanced by using it in combination with one or more of the concomitant drug(s) mentioned above (multi-agent co-administration).

[0393]

Examples of the "hormonal therapeutic agents" include fosfestrol, diethylstylbestrol, chlorotrianisene, medroxyprogesterone acetate, megestrol acetate, chlormadinone acetate, cyproterone acetate, danazol, dienogest, asoprisnil, allylestrenol, gestrinone, nomegestrol, tadenan, mepartricin, raloxifene, ormeloxifene, levormeloxifene, anti-estrogens (e.g., tamoxifen citrate, toremifene citrate, and the like), ER down-regulator (e.g., fulvestrant, and the like), human menopausal gonadotrophin, follicle stimulating hormone, pill preparations, mepitiostane, testrolactone, aminoglutethimide, LH-RH agonists (e.g., goserelin acetate, buserelin,

leuprorelin, and the like), droloxifene, epitiostanol, ethinylestradiol sulfonate, aromatase inhibitors (e.g., fadrozole hydrochloride, anastrozole, retrozole, exemestane, vorozole, formestane, and the like), anti-androgens (e.g., flutamide, bicartamide, nilutamide, and the like), 5α-reductase inhibitors (e.g., finasteride, dutasteride, epristeride, and the like), adrenocorticohormone drugs (e.g., dexamethasone, prednisolone, betamethasone, triamcinolone, and the like), androgen synthesis inhibitors (e.g., abiraterone, and the like), retinoid and drugs that retard retinoid metabolism (e.g., liarozole, and the like), etc. and LH-RH agonists (e.g., goserelin acetate, buserelin, leuprorelin etc.) are preferable.

[0394]

As examples of said "chemotherapeutic agents", there may be mentioned alkylating agents, antimetabolites, anticancer antibiotics, plant-derived anticancer agents, and the like.

[0395]

Examples of the "alkylating agents" include nitrogen mustard, nitrogen mustard-N-oxide hydrochloride, chlorambutyl, cyclophosphamide, ifosfamide, thiotepa, carboquone, improsulfan tosylate, busulfan, nimustine hydrochloride, mitobronitol, melphalan, dacarbazine, ranimustine, sodium estramustine phosphate, triethylenemelamine, carmustine, lomustine, streptozocin, pipobroman, etoglucid, carboplatin, cisplatin, miboplatin, nedaplatin, oxaliplatin, altretamine, ambamustine, dibrospidium hydrochloride, fotemustine, prednimustine, pumitepa, ribomustin, temozolomide, treosulphan, trophosphamide, zinostatin stimalamer, adozelesin, cystemustine, bizelesin, and the like.

[0396]

Examples of the "antimetabolites" include mercaptopurine, 6-mercaptopurine riboside, thioinosine, methotrexate, enocitabine, cytarabine, cytarabine ocfosfate, ancitabine hydrochloride, 5-FU drugs (e.g., fluorouracil, tegafur, UFT,

doxifluridine, carmofur, gallocitabine, emmitefur, and the like), aminopterine, leucovorin calcium, tabloid, butocine, folinate calcium, levofolinate calcium, cladribine, emitefur, fludarabine, gemcitabine, hydroxycarbamide, pentostatin, piritrexim, idoxuridine, mitoguazone, thiazophrine, ambamustine, and the like.

[0397]

Examples of the "anticancer antibiotics" include actinomycin-D, actinomycin-C, mitomycin-C, chromomycin-A3, bleomycin hydrochloride, bleomycin sulfate, peplomycin sulfate, daunorubicin hydrochloride, doxorubicin hydrochloride, aclarubicin hydrochloride, pirarubicin hydrochloride, epirubicin hydrochloride, neocarzinostatin, mithramycin, sarcomycin, carzinophilin, mitotane, zorubicin hydrochloride, mitoxantrone hydrochloride, idarubicin hydrochloride, and the like.

[0398]

Examples of the "plant-derived anticancer agents" include etoposide, etoposide phosphate, vinblastine sulfate, vincristine sulfate, vindesine sulfate, teniposide, paclitaxel, docetaxel, vinorelbine, and the like.

[0399]

Examples of said "immunotherapeutic agents (BRM)" include picibanil, krestin, sizofiran, lentinan, ubenimex, interferons, interleukins, macrophage colony-stimulating factor, granulocyte colony-stimulating factor, erythropoietin, lymphotoxin, BCG vaccine, *Corynebacterium parvum*, levamisole, polysaccharide K, procodazole, and the like.

[0400]

As the "growth factor" in said "medicaments inhibiting the action of cell growth factors or receptors", there may be mentioned any substances that promote cell proliferation, which are normally peptides having a molecular weight of not more than 20,000 that are capable of exhibiting their activity at low concentrations by binding to a receptor, including (1)

EGF (epidermal growth factor) or substances possessing substantially the same activity as it [e.g., EGF, heregulin (HER2 ligand), and the like], (2) insulin or substances possessing substantially the same activity as it [e.g., insulin, IGF (insulin-like growth factor)-1, IGF-2, and the like], (3) FGF (fibroblast growth factor) or substances possessing substantially the same activity as it [e.g., acidic FGF, basic FGF, KGF (keratinocyte growth factor), FGF-10, and the like], (4) other cell growth factors [e.g., CSF (colony stimulating factor), EPO (erythropoietin), IL-2 (interleukin-2), NGF (nerve growth factor), PDGF (platelet-derived growth factor), TGFβ (transforming growth factor β), HGF (hepatocyte growth factor), VEGF (vascular endothelial growth factor), and the like], and the like.

[0401]

Examples of said "growth factor receptors" include any receptors capable of binding to the aforementioned cell growth factors, including EGF receptor, heregulin receptor (HER2), insulin receptor, IGF receptor, FGF receptor-1 or FGF receptor-2, and the like.

[0402]

Examples of said "medicament that inhibits the action of cell growth factor" include trastuzumab (Herceptin (trade mark); HER2 antibody), imatinib mesylate, ZD1839 or cetuximab, antibody against VEGF (e.g., bevacizumab), antibody against VEGF receptor, gefitinib, erlotinib and the like.

[0403]

In addition to the aforementioned drugs, L-asparaginase, aceglatone, procarbazine hydrochloride, protoporphyrin-cobalt complex salt, mercuric hematoporphyrin-sodium, topoisomerase I inhibitors (e.g., irinotecan, topotecan, and the like), topoisomerase II inhibitors (e.g., sobuzoxane, and the like), differentiation inducers (e.g., retinoid, vitamin D, and the like), angiogenesis inhibitors (e.g., thalidomide, SU11248, and the like), α-blockers (e.g., tamsulosin hydrochloride,

naftopidil, urapidil, alfuzosin, terazosin, prazosin, silodosin, and the like) serine/threonine kinase inhibitor, endothelin receptor antagonist (e.g., atrasentan, and the like), proteasome inhibitor (e.g., bortezomib, and the like), Hsp 90 inhibitor (e.g., 17-AAG, and the like), spironolactone, minoxidil, 11α-hydroxyprogesterone, bone resorption inhibiting/metastasis suppressing agent (e.g., zoledronic acid, alendronic acid, pamidronic acid, etidronic acid, ibandronic acid, clodronic acid) and the like can be used.

[0404]

While the HER2 inhibitor of the present invention or Lapatinib can be concomitantly used with trastuzumab, it is most preferably used in place of trastuzumab against cancer identified to be resistant to trastuzumab by the method of examining the sensitivity of HER2 expression cancer.

[0405]

The present invention is explained in more detail in the following by referring Examples, which are mere examples and do not at all limit the scope of the present invention.

Examples

[0406]

Example 1

Used were BT474 cells (American Type Culture Collection, HTB-20, J Natl Cancer Inst 61: 967-978 (1978)), which are highly sensitive to trastuzumab, and trastuzumab low sensitive BT-474 cells which were obtained by culturing the BT474 cells highly sensitive to trastuzumab in RPMI complete medium containing 5 μg/mL trastuzumab for 3 months or longer. LIMK1 gene was knocked down by the following RNAi method. Three kinds of Sthealth RNAis (LIMK1 Stealth Select 3 RNAi, Invitrogen, HSS140837:HSS140836:HSS141043) corresponding to LIMK1 gene and Lipofectamin RNAiMAX (Invtrogen, 13778-150) were mixed with Opti-MEM(R) I Reduced-Serum Medium (Invitrogen, 31985-070) to 36.7 nM x3 (total 110 nM) and 11 μL/mL,

respectively. After standing for 20 min at room temperature, the Sthealth RNAis were mixed at 1:11 liquid volume with respective BT-474 cell suspensions adjusted to 22,000 cells/mL in the culture medium (final concentration; Stealth RNAis total 10 nM, Lipofectamin RNAiMAX 1 μL/mL, 20,000 cells/mL). As a control, similar operation was performed using Stealth™ RNAi Negative Control Duplexes Complete Kit (Invitrogen, 12935-100). Respective BT-474 cells mixed with Stealth RNAis were seeded in a 96 well plate (Nunc) at 3000 cells/150 μL/well and cultured 2-overnights, and trastuzumab (Rosh) was added at 50 μL/well to respective final concentrations. After culture for 5 days at 37°C, 5% CO_2, the number of viable cells was counted.

[0407]

When treated with control siRNA, the growth was suppressed by about 70% in the high sensitive cell line and about 30% in the low sensitive cell line by the addition of trastuzumab (3 μg/mL) as compared to without addition of trastuzumab. In contrast, with knockdown of LIMK1 by LIMK1 siRNA, the growth was suppressed by about 80% in the low sensitive cell line, and the growth was completely suppressed in the high sensitive cell line. Therefrom it was revealed that inhibition of LIMK1 enhances the sensitivity to trastuzumab.

[0408]

Example 2

Used were BT474 cells (American Type Culture Collection, HTB-20, J Natl Cancer Inst 61: 967-978 (1978)), which are highly sensitive to trastuzumab, and trastuzumab low sensitive BT-474 cells which were obtained by culturing the BT474 cells highly sensitive to trastuzumab in RPMI complete medium containing 5 μg/mL trastuzumab for 3 months or longer. PAK1 gene was knocked down by the following RNAi method. Two kinds of Sthealth RNAis (PAK1 Validated Stealth RNAi DuoPac, Invitrogen, 45-1676) corresponding to PAK1 gene and

Lipofectamin RNAiMAX (Invtrogen, 13778-150) were mixed with Opti-MEM(R) I Reduced-Serum Medium (Invitrogen, 31985-070) to 55 nM x2 (total 110 nM) and 11 μL/mL, respectively. After standing for 20 min at room temperature, the Sthealth RNAis were mixed at 1:11 liquid volume with respective BT-474 cell suspensions adjusted to 22,000 cells/mL in the culture medium (final concentration; Stealth RNAis total 10 nM, Lipofectamin RNAiMAX 1 μL/mL, 20,000 cells/mL). As a control, similar operation was performed using Stealth™ RNAi Negative Control Duplexes Complete Kit (Invitrogen, 12935-100). Respective BT-474 cells mixed with Stealth RNAis were seeded in a 96 well plate (Nunc) at 3000 cells/150 μL/well and cultured 2-overnights, and trastuzumab (Rosh) was added at 50 μL/well to respective final concentrations. After culture for 5 days at 37°C, 5% CO_2, the number of viable cells was counted.

[0409]

When treated with control siRNA, the growth was suppressed by about 70% in the high sensitive cell line and about 30% in the low sensitive cell line by the addition of trastuzumab (3 μg/mL) as compared to without addition of trastuzumab. In contrast, with knockdown of PAK1 by PAK1 siRNA, the growth was suppressed by about 50% in the low sensitive cell line, and the growth was completely suppressed in the high sensitive cell line. Therefrom it was revealed that inhibition of PAK1 enhances the sensitivity to trastuzumab.

[0410]

Example 3

Used were BT474 cells (American Type Culture Collection, HTB-20, J Natl Cancer Inst 61: 967-978 (1978)), which are highly sensitive to trastuzumab, and trastuzumab low sensitive BT-474 cells which were obtained by culturing the BT474 cells highly sensitive to trastuzumab in RPMI complete medium containing 5 μg/mL trastuzumab for 3 months or longer. Cofilin1 gene was knocked down by the following RNAi method. Three kinds of Sthealth RNAis (CFL Stealth Select 3 RNAi,

Invitrogen, HSS141559:HSS141560:HSS141561) corresponding to cofilin1 gene and Lipofectamin RNAiMAX (Invtrogen, 13778-150) were mixed with Opti-MEM(R) I Reduced-Serum Medium (Invitrogen, 31985-070) to 36.7 nM x3 (total 110 nM) and 11 μL/mL, respectively. After standing for 20 min at room temperature, the Sthealth RNAis were mixed at 1:11 liquid volume with respective BT-474 cell suspensions adjusted to 22,000 cells/mL in the culture medium (final concentration; Stealth RNAis total 10 nM, Lipofectamin RNAiMAX 1 μL/mL, 20,000 cells/mL). As a control, similar operation was performed using Stealth™ RNAi Negative Control Duplexes Complete Kit (Invitrogen, 12935-100). Respective BT-474 cells mixed with Stealth RNAis were seeded in a 96 well plate (Nunc) at 3000 cells/150 μL/well and cultured 2-overnights, and trastuzumab (Rosh) was added at 50 μL/well to respective final concentrations. After culture for 5 days at 37°C, 5% CO_2, the number of viable cells was counted.

[0411]

When treated with control siRNA, the growth was suppressed by about 70% in the high sensitive cell line and about 30% in the low sensitive cell line by the addition of trastuzumab (3 μg/mL) as compared to without addition of trastuzumab. In contrast, with knockdown of cofilin1 by cofilin1 siRNA, the growth was suppressed by about 80% in the high sensitive cell line and by about 50% in the low sensitive cell line. Therefrom it was revealed that inhibition of cofilin1 enhances the sensitivity to trastuzumab.

[0412]

Example 4

Used were BT474 cells (American Type Culture Collection, HTB-20, J Natl Cancer Inst 61: 967-978 (1978)), which are highly sensitive to trastuzumab, and trastuzumab low sensitive BT-474 cells which were obtained by culturing the BT474 cells highly sensitive to trastuzumab in RPMI complete medium containing 5 μg/mL trastuzumab for 3 months or longer. The

gene was knocked down by the following RNAi method. Three kinds of Sthealth RNAis (RHO Stealth Select 3 RNAi, Invitrogen, HSS140837:HSS140836:HSS141043) corresponding to Rho gene and Lipofectamin RNAiMAX (Invtrogen, 13778-150) were mixed with Opti-MEM(R) I Reduced-Serum Medium (Invitrogen, 31985-070) to 36.7 nM x3 (total 110 nM) and 11 µL/mL, respectively. After standing for 20 min at room temperature, the Sthealth RNAis were mixed at 1:11 liquid volume with respective BT-474 cell suspensions adjusted to 22,000 cells/mL in the culture medium (final concentration; Stealth RNAis total 10 nM, Lipofectamin RNAiMAX 1 µL/mL, 20,000 cells/mL). As a control, similar operation was performed using Stealth™ RNAi Negative Control Duplexes Complete Kit (Invitrogen, 12935-100). Respective BT-474 cells mixed with Stealth RNAis were seeded in a 96 well plate (Nunc) at 3000 cells/150 µL/well and cultured 2-overnights, and trastuzumab (Rosh) was added at 50 µL/well to respective final concentrations. After culture for 5 days at 37°C, 5% CO_2, the number of viable cells was counted.

[0413]

When treated with control siRNA, the growth was suppressed by about 40% in the high sensitive cell line and about 10% in the low sensitive cell line by the addition of trastuzumab (3 µg/mL) as compared to without addition of trastuzumab. In contrast, with knockdown of Rho by Rho siRNA, the growth was suppressed by about 30% in the low sensitive cell line, and by about 70% in the high sensitive cell line. Therefrom it was revealed that inhibition of Rho enhances the sensitivity to the HER2 inhibitor.

[0414]

Example 5

Used were BT474 cells (American Type Culture Collection, HTB-20, J Natl Cancer Inst 61: 967-978 (1978)), which are highly sensitive to trastuzumab, and trastuzumab low sensitive BT-474 cells which were obtained by culturing the BT474 cells highly sensitive to trastuzumab in RPMI complete medium

containing 5 μg/mL trastuzumab for 3 months or longer. ROCK1 gene was knocked down by the following RNAi method. Two kinds of Sthealth RNAis (PAK1 Validated Stealth RNAi DuoPac, Invitrogen, 45-1676) corresponding to ROCK1 gene and Lipofectamin RNAiMAX (Invtrogen, 13778-150) were mixed with Opti-MEM(R) I Reduced-Serum Medium (Invitrogen, 31985-070) to 55 nM x2 (total 110 nM) and 11 μL/mL, respectively. After standing for 20 min at room temperature, the Sthealth RNAis were mixed at 1:11 liquid volume with respective BT-474 cell suspensions adjusted to 22,000 cells/mL in the culture medium (final concentration; Stealth RNAis total 10 nM, Lipofectamin RNAiMAX 1 μL/mL, 20,000 cells/mL). As a control, similar operation was performed using Stealth™ RNAi Negative Control Duplexes Complete Kit (Invitrogen, 12935-100). Respective BT-474 cells mixed with Stealth RNAis were seeded in a 96 well plate (Nunc) at 3000 cells/150 μL/well and cultured 2-overnights, and trastuzumab (Rosh) was added at 50 μL/well to respective final concentrations. After culture for 5 days at 37°C, 5% CO_2, the number of viable cells was counted.

[0415]

When treated with control siRNA, the growth was suppressed by about 40% in the high sensitive cell line and about 10% in the low sensitive cell line by the addition of trastuzumab (3 μg/mL) as compared to without addition of trastuzumab. In contrast, with knockdown of ROCK1 by ROCK1 siRNA, the growth was suppressed by about 30% in the low sensitive cell line, and by about 75% in the high sensitive cell line. Therefrom it was revealed that inhibition of ROCK1 enhances the sensitivity to the HER2 inhibitor.

[0416]

Example 6

Used were BT474 cells (American Type Culture Collection, HTB-20, J Natl Cancer Inst 61: 967-978 (1978)), which are highly sensitive to trastuzumab, and trastuzumab low sensitive BT-474 cells which were obtained by culturing the BT474 cells

highly sensitive to trastuzumab in RPMI complete medium containing 5 μg/mL trastuzumab for 3 months or longer. ROCK2 gene was knocked down by the following RNAi method. Three kinds of Sthealth RNAis (CFL1 Stealth Select 3 RNAi, Invitrogen, HSS141559:HSS141560:HSS141561) corresponding to ROCK2 gene and Lipofectamin RNAiMAX (Invtrogen, 13778-150) were mixed with Opti-MEM(R) I Reduced-Serum Medium (Invitrogen, 31985-070) to 36.7 nM x3 (total 110 nM) and 11 μL/mL, respectively. After standing for 20 min at room temperature, the Sthealth RNAis were mixed at 1:11 liquid volume with respective BT-474 cell suspensions adjusted to 22,000 cells/mL in the culture medium (final concentration; Stealth RNAis total 10 nM, Lipofectamin RNAiMAX 1 μL/mL, 20,000 cells/mL). As a control, similar operation was performed using Stealth™ RNAi Negative Control Duplexes Complete Kit (Invitrogen, 12935-100). Respective BT-474 cells mixed with Stealth RNAis were seeded in a 96 well plate (Nunc) at 3000 cells/150 μL/well and cultured 2-overnights, and trastuzumab (Rosh) was added at 50 μL/well to respective final concentrations. After culture for 5 days at 37°C, 5% CO_2, the number of viable cells was counted.

[0417]

When treated with control siRNA, the growth was suppressed by about 40% in the high sensitive cell line and about 10% in the low sensitive cell line by the addition of trastuzumab (3 μg/mL) as compared to without addition of trastuzumab. In contrast, with knockdown of ROCK2 by ROCK2 siRNA, the growth was suppressed by about 50% in the low sensitive cell line, and the growth was completely suppressed in the high sensitive cell line. Therefrom it was revealed that inhibition of ROCK2 enhances the sensitivity to the HER2 inhibitor.

[0418]

Example 7

Used were BT474 cells (American Type Culture Collection,

HTB-20, J Natl Cancer Inst 61: 967-978 (1978)), which are highly sensitive to trastuzumab, and trastuzumab low sensitive BT-474 cells which were obtained by culturing the BT474 cells highly sensitive to trastuzumab in RPMI complete medium containing 5 μg/mL trastuzumab for 3 months or longer. Respective BT-474 cells were seeded in a 96 well plate (Nunc) at 3000 cells/150 μL/well and cultured 2-overnights, and trastuzumab (Rosh) or compound A were added by 50 μL/well to respective final concentrations. After culture for 5 days at 37°C, 5% CO_2, the number of viable cells was counted.

[0419]

The growth was suppressed by about 50% in the high sensitive cell line and about 10% in the low sensitive cell line by the addition of trastuzumab (3 μg/mL) as compared to without addition of trastuzumab. In contrast, by the addition of compound A, a similar level of concentration-dependent growth suppression was observed in both the low sensitive cell line and the high sensitive cell line, and by the addition of compound A (1 μmol/L), complete suppression of growth was observed in both the low sensitive cell line and the high sensitive cell line.

[0420]

Example 8

Used were BT474 cells (American Type Culture Collection, HTB-20, J Natl Cancer Inst 61: 967-978 (1978)), which are highly sensitive to trastuzumab, and trastuzumab low sensitive BT-474 cells which were obtained by culturing the BT474 cells highly sensitive to trastuzumab in RPMI complete medium containing 5 μg/mL trastuzumab for 3 months or longer. Respective BT-474 cells were seeded in a 96 well plate (Nunc) at 3000 cells/150 μL/well and cultured 2-overnights, and trastuzumab (Rosh) or lapatinib were added by 50 μL/well to respective final concentrations. After culture for 5 days at 37°C, 5% CO_2, the number of viable cells was counted.

[0421]

The growth was suppressed by about 50% in the high sensitive cell line and about 10% in the low sensitive cell line by the addition of trastuzumab (3 μg/mL) as compared to without addition of trastuzumab. In contrast, by the addition of lapatinib, a similar level of concentration-dependent growth suppression was observed in both the low sensitive cell line and the high sensitive cell line, and by the addition of lapatinib (1 μmol/L), complete suppression of growth was observed in both the low sensitive cell line and the high sensitive cell line.

Industrial Applicability

[0422]

The agent for preventing or treating cancer of the present invention, which comprises one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a Rho inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor, can be used effectively for the prophylaxis or treatment of cancer not only by a single use but also by combining with a conventional HER2 inhibitor.

[0423]

This application is based on a patent application No. 2007-161769 filed in Japan, the contents of which are incorporated in full herein by this reference.

Claims

1. An agent for preventing or treating a trastuzumab-resistant cancer, comprising one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a RHO inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor.

2. The agent according to claim 1, comprising a cofilin inhibitor.

3. The agent according to claim 1, comprising a PAK1 inhibitor.

4. The agent according to claim 1, comprising a LIMK inhibitor.

5. The agent according to claim 1, comprising a RHO inhibitor.

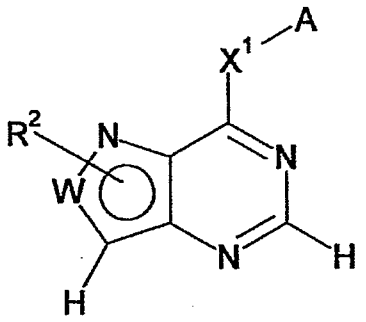
6. The agent according to claim 1, comprising a ROCK1 inhibitor.

7. The agent according to claim 1, comprising a ROCK2 inhibitor.

8. A combination drug comprising (1) a HER2 inhibitor and (2) one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a RHO inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor.

9. The drug according to claim 8, wherein the HER2 inhibitor is trastuzumab or lapatinib.

10. The drug according to claim 8, wherein the HER2 inhibitor is a compound represented by the formula



(I)

wherein W is $C(R^1)$ or N,

A is an optionally substituted aryl group or an optionally substituted heteroaryl group,

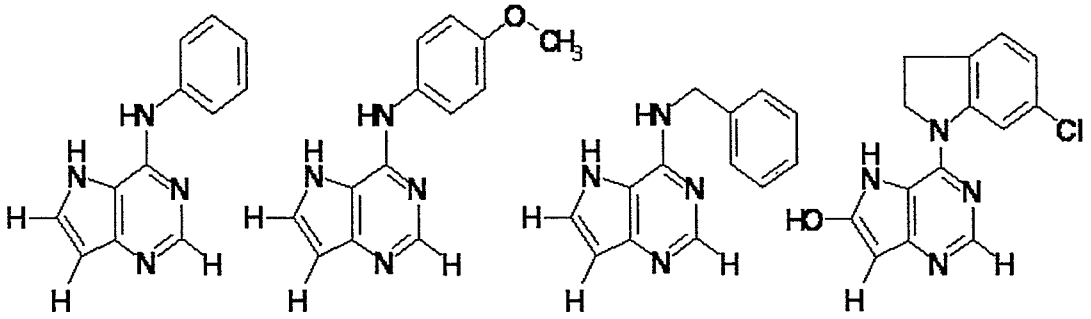
X^1 is $-NR^3-Y^1-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-CHR^3-$

wherein R^3 is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or R^3 is optionally bonded to a carbon atom or hetero atom on an aryl group or heteroaryl group for A to form an optionally substituted ring structure,

Y^1 is a single bond or C_{1-4} alkylene or $-O-(C_{1-4}$ alkylene$)-$, each of which is optionally substituted,

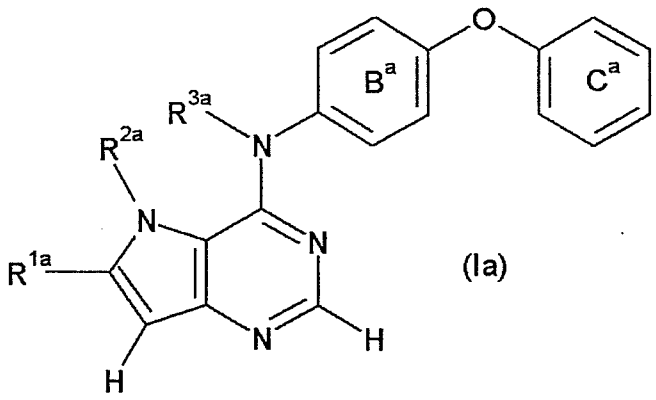
R^1 is a hydrogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom, and R^2 is a hydrogen atom, or an optionally substituted group bonded via a carbon atom or a sulfur atom, or

R^1 and R^2, or R^2 and R^3 are optionally bonded to each other to form an optionally substituted ring structure, except a compound represented by the formula



or a salt thereof.

11. The drug according to claim 8, wherein the HER2 inhibitor is a compound represented by the formula



(Ia)

wherein

R^{1a} is a hydrogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

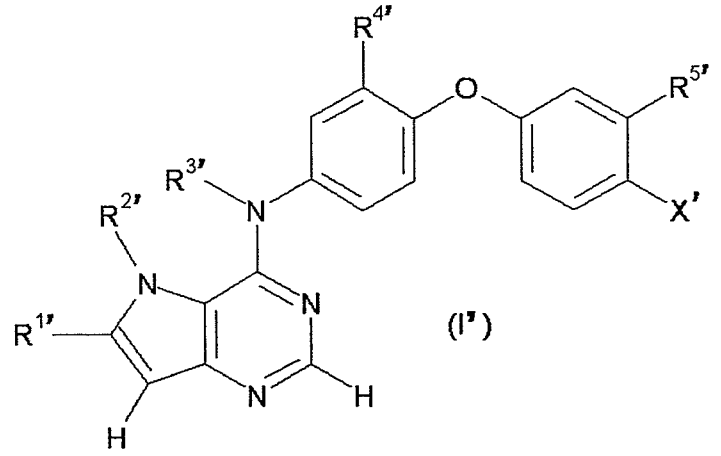
R^{2a} is an optionally substituted group bonded via a carbon atom or a sulfur atom, or

R^{1a} and R^{2a}, or R^{2a} and R^{3a} are optionally bonded to each other to form an optionally substituted ring structure,

R^{3a} is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or R^{3a} is optionally bonded via a carbon atom of the adjacent phenyl group to form an optionally substituted ring structure,

B^a is an optionally substituted benzene ring, and C^a is an optionally substituted C_{6-18} aryl group, or a salt thereof.

12. The drug according to claim 8, wherein the HER2 inhibitor is a compound represented by the formula



(I')

wherein

$R^{1'}$ is a hydrogen atom,

$R^{2'}$ is a C_{1-6} alkyl group substituted by a group represented by $-NR^{6'}-CO-(CH_2)_n-SO_2-$(optionally halogenated C_{1-4} alkyl) wherein n is an integer of 1 to 4, $R^{6'}$ is a hydrogen atom or a C_{1-4} alkyl group, wherein $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

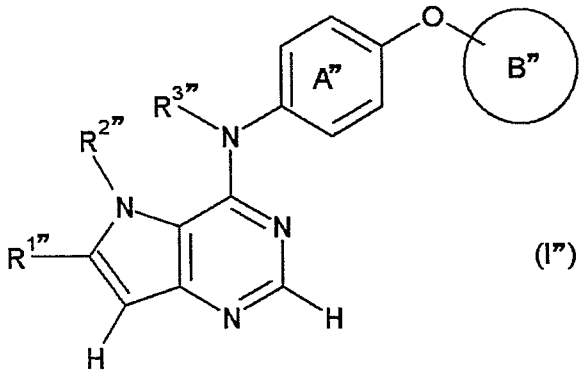
$R^{3'}$ is a hydrogen atom or a C_{1-6} alkyl group,

$R^{4'}$ is a halogen atom or a C_{1-6} alkyl group,

$R^{5'}$ is a halogen atom or a C_{1-6} alkyl group, and

X' is a hydrogen atom or a halogen atom, except N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide, or a salt thereof.

13. The drug according to claim 8, wherein the HER2 inhibitor is a compound represented by the formula



(I")

wherein

$R^{1''}$ is a hydrogen atom, a halogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

$R^{2''}$ is a hydrogen atom, or an optionally substituted group bonded via a carbon atom or a sulfur atom,

or $R^{1''}$ and $R^{2''}$, or $R^{2''}$ and $R^{3''}$ are optionally bonded to each other to form an optionally substituted ring structure;

$R^{3''}$ is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or

$R^{3''}$ is optionally bonded to a carbon atom of ring A" to form an optionally substituted ring structure;

ring A" is an optionally substituted benzene ring;

ring B" is (i) an optionally substituted fused ring, or

(ii) a pyridine ring having optionally substituted carbamoyl wherein the pyridine ring is optionally further substituted, or a salt thereof.

14. The drug according to claim 8, wherein the HER2 inhibitor is N-{2-[4-({3-chloro-4-[3-(trifluoromethyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide or a salt thereof.

15. The drug according to claim 8, which is an agent for preventing or treating HER2-expressing cancer.

16. A method of preventing or treating trastuzumab-resistant cancer, which comprises inhibiting one or more selected from cofilin, PAK1, LIMK, RHO, ROCK1 and ROCK2.

17. The method according to claim 16, which comprises administering an effective amount of one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a RHO inhibitor, a ROCK1 inhibitor and a ROCK2

inhibitor to a mammal.

18. Use of one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a RHO inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor for the production of an agent for preventing or treating a trastuzumab-resistant cancer.

19. A method of examining the sensitivity of a HER2-expressing cancer to a HER2 inhibitor, comprising measuring the expression or activation state of one or more selected from cofilin, PAK1, LIMK, RHO, ROCK1 and ROCK2 in a sample collected from an animal having the cancer.

20. A method of treating a cancer in an animal judged to be low sensitive to a HER2 inhibitor by the method according to claim 19, which comprises administering an effective amount of each of (1) a HER2 inhibitor, and (2) one or more medicaments selected from a cofilin inhibitor, a PAK1 inhibitor, a LIMK inhibitor, a RHO inhibitor, a ROCK1 inhibitor and a ROCK2 inhibitor to the animal.

21. A method of screening for a drug for the prophylaxis or treatment of a trastuzumab-resistant cancer, comprising measuring and comparing the expression, activation state or activity of one or more selected from cofilin, PAK1, LIMK, RHO, ROCK1 and ROCK2 in a cell in the presence or absence of a test compound.

22. An agent for preventing or treating a trastuzumab-resistant cancer, comprising N-{2-[4-({3-chloro-4-[3-(trifluoromethyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide or a salt thereof.

23. A method of treating a trastuzumab-resistance cancer in a mammal, comprising administering an effective amount of N-{2-[4-({3-chloro-4-[3-(trifluoromethyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide or a salt thereof to the animal.

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tcc ctg ggc atc atg gcc atc gaa atg att gaa ggg gag cct cca tac 1750
Ser Leu Gly Ile Met Ala Ile Glu Met Ile Glu Gly Glu Pro Pro Tyr
450 455 460

ctc aat gaa aac cct ctg aga gcc ttg tac ctc att gcc acc aat ggg 1798
Leu Asn Glu Asn Pro Leu Arg Ala Leu Tyr Leu Ile Ala Thr Asn Gly
465 470 475 480

acc cca gaa ctt cag aac cca gag aag ctg tca gct atc ttc cgg gac 1846
Thr Pro Glu Leu Gln Asn Pro Glu Lys Leu Ser Ala Ile Phe Arg Asp
485 490 495

ttt ctg aac cgc tgt ctc gag atg gat gtg gag aag aga ggt tca gct 1894
Phe Leu Asn Arg Cys Leu Glu Met Asp Val Glu Lys Arg Gly Ser Ala
500 505 510

aaa gag ctg cta cag cat caa ttc ctg aag att gcc aag ccc ctc tcc 1942
Lys Glu Leu Leu Gln His Gln Phe Leu Lys Ile Ala Lys Pro Leu Ser
515 520 525

agc ctc act cca ctg att gct gca gct aag gag gca aca aag aac aat 1990
Ser Leu Thr Pro Leu Ile Ala Ala Ala Lys Glu Ala Thr Lys Asn Asn
530 535 540

cac taaaaccaca ctcaccccag cctcattgtg ccaagccttc tgtgagataa 2043
His
545

atgcacattt cagaaattcc aactcctgat gccctcttct ccttgccttg cttctcccat 2103

ttcctgatct agcactcctc aagactttga tccttggaaa ccgtgtgtcc agcattgaag 2163

agaactgcaa ctgaatgact aatcagatga tggccatttc taaataagga atttcctccc 2223

aattcatgga tatgagggtg gtttatgatt aagggtttat ataaataaat gtttctagtc 2283

ttccgtgtgt caaaatcctc acctccttca taaccatctc ccacaattaa ttcttgacta 2343

tataaattta tggtttgata atattatcaa tttgtaatca attgagattt ctttagtgct 2403

tgcttttctg tgactcaact gcccagacac ctcattgtac ttgaaaactg gaacagcttg 2463

ggaatgccat ggggtttgat aatctgccag ggacatgaag aggctcagct tcctggacca 2523

tgactttggc tcagctgatc ctgacatggg agaacaacca catttttctt tgtgtgtgct 2583

tctagcagct gttcgggagg accttgaccc aatagtgttc ccatgctgtt tcttgtgaaa 2643

tgctctcggc tatgtagcag cttttgattc cctgcatacc ctaggctgct gcccctatcc 2703

tgtcccttgt ttataacatt gagaggtttt ctagggcaca tactgagtga gagcagtgtt 2763

gagaagtcgg ggaaaatggt gactactttt agagcaaggc tgggcatcag cacctgtcca 2823

gctctacttg tgtgatgttt caggaactca gcccctttt ctgcctagga taaggagctg 2883

aaagattaac ttggatcttc taatggtcca aatcttttgg tcacaataaa gagtctccaa 2943

attagagact gcatgttagt tctggatgga tttggtggcc tgacatgata ccctgccagc 3003

tgtgagggga ccccgttttt aagatgcatg gccaagctct ctgcaaatgg aaatgcttac 3063

actgggtgtt ggggatgttt gctacctcct gctatttttg tggttttggt tctcccacta 3123

tggtaggacc cctggccagc attgtggctt gtcatgtcag ccccattgac taccttctca 3183

tgctctgagg tactactgcc tctgcagcac aaatttctat ttctgtcaat aaaaggagat 3243

gaaaatattc taaaaaaaaa a 3264

<210> 6
<211> 545
<212> PRT
<213> Homo sapiens

<400> 6

Met Ser Asn Asn Gly Leu Asp Ile Gln Asp Lys Pro Pro Ala Pro Pro
1 5 10 15

Met Arg Asn Thr Ser Thr Met Ile Gly Ala Gly Ser Lys Asp Ala Gly
20 25 30

Thr Leu Asn His Gly Ser Lys Pro Leu Pro Pro Asn Pro Glu Glu Lys
35 40 45

Lys Lys Lys Asp Arg Phe Tyr Arg Ser Ile Leu Pro Gly Asp Lys Thr
50 55 60

Asn Lys Lys Lys Glu Lys Glu Arg Pro Glu Ile Ser Leu Pro Ser Asp
65 70 75 80

Phe Glu His Thr Ile His Val Gly Phe Asp Ala Val Thr Gly Glu Phe
85 90 95

Thr Gly Met Pro Glu Gln Trp Ala Arg Leu Leu Gln Thr Ser Asn Ile
100 105 110

Thr Lys Ser Glu Gln Lys Lys Asn Pro Gln Ala Val Leu Asp Val Leu
115 120 125

Glu Phe Tyr Asn Ser Lys Lys Thr Ser Asn Ser Gln Lys Tyr Met Ser
130 135 140

Phe Thr Asp Lys Ser Ala Glu Asp Tyr Asn Ser Ser Asn Ala Leu Asn
145 150 155 160

Val Lys Ala Val Ser Glu Thr Pro Ala Val Pro Pro Val Ser Glu Asp
165 170 175

Glu Asp Asp Asp Asp Asp Asp Ala Thr Pro Pro Pro Val Ile Ala Pro
180 185 190

Arg Pro Glu His Thr Lys Ser Val Tyr Thr Arg Ser Val Ile Glu Pro
195 200 205

Leu Pro Val Thr Pro Thr Arg Asp Val Ala Thr Ser Pro Ile Ser Pro
210 215 220

Thr Glu Asn Asn Thr Thr Pro Pro Asp Ala Leu Thr Arg Asn Thr Glu
225 230 235 240

Lys Gln Lys Lys Lys Pro Lys Met Ser Asp Glu Glu Ile Leu Glu Lys
245 250 255

Leu Arg Ser Ile Val Ser Val Gly Asp Pro Lys Lys Lys Tyr Thr Arg
260 265 270

Phe Glu Lys Ile Gly Gln Gly Ala Ser Gly Thr Val Tyr Thr Ala Met
275 280 285

Asp Val Ala Thr Gly Gln Glu Val Ala Ile Lys Gln Met Asn Leu Gln
290 295 300

Gln Gln Pro Lys Lys Glu Leu Ile Ile Asn Glu Ile Leu Val Met Arg
305 310 315 320

Glu Asn Lys Asn Pro Asn Ile Val Asn Tyr Leu Asp Ser Tyr Leu Val
325 330 335

Gly Asp Glu Leu Trp Val Val Met Glu Tyr Leu Ala Gly Gly Ser Leu
340 345 350

Thr Asp Val Val Thr Glu Thr Cys Met Asp Glu Gly Gln Ile Ala Ala
355 360 365

Val Cys Arg Glu Cys Leu Gln Ala Leu Glu Phe Leu His Ser Asn Gln
370 375 380

Val Ile His Arg Asp Ile Lys Ser Asp Asn Ile Leu Leu Gly Met Asp
385 390 395 400

Gly Ser Val Lys Leu Thr Asp Phe Gly Phe Cys Ala Gln Ile Thr Pro
405 410 415

Glu Gln Ser Lys Arg Ser Thr Met Val Gly Thr Pro Tyr Trp Met Ala
420 425 430

Pro Glu Val Val Thr Arg Lys Ala Tyr Gly Pro Lys Val Asp Ile Trp
435 440 445

Ser Leu Gly Ile Met Ala Ile Glu Met Ile Glu Gly Glu Pro Pro Tyr
450 455 460

Leu Asn Glu Asn Pro Leu Arg Ala Leu Tyr Leu Ile Ala Thr Asn Gly
465 470 475 480

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Thr Pro Glu Leu Gln Asn Pro Glu Lys Leu Ser Ala Ile Phe Arg Asp
                485                 490                 495

Phe Leu Asn Arg Cys Leu Glu Met Asp Val Glu Lys Arg Gly Ser Ala
            500                 505                 510

Lys Glu Leu Leu Gln His Gln Phe Leu Lys Ile Ala Lys Pro Leu Ser
        515                 520                 525

Ser Leu Thr Pro Leu Ile Ala Ala Ala Lys Glu Ala Thr Lys Asn Asn
    530                 535                 540

His
545
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<210> 7
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<212> DNA
<213> Homo sapiens

<220>
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<222> (166)..(2106)

<400> 7

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ccgcgccctc cgcccccgcc tccccgggcc ggcggcggtg ggcgagctcg cgggccccgc     120

cgcccccagc cccagccccg ccgggccccg ccccccgtcg agtgc atg agg ttg acg     177
                                                  Met Arg Leu Thr
                                                  1

cta ctt tgt tgc acc tgg agg gaa gaa cgt atg gga gag gaa gga agc       225
Leu Leu Cys Cys Thr Trp Arg Glu Glu Arg Met Gly Glu Glu Gly Ser
5                   10                  15                  20

gag ttg ccc gtg tgt gca agc tgc ggc cag agg atc tat gat ggc cag      273
Glu Leu Pro Val Cys Ala Ser Cys Gly Gln Arg Ile Tyr Asp Gly Gln
                25                  30                  35

tac ctc cag gcc ctg aac gcg gac tgg cac gca gac tgc ttc agg tgt      321
Tyr Leu Gln Ala Leu Asn Ala Asp Trp His Ala Asp Cys Phe Arg Cys
            40                  45                  50

tgt gac tgc agt gcc tcc ctg tcg cac cag tac tat gag aag gat ggg      369
Cys Asp Cys Ser Ala Ser Leu Ser His Gln Tyr Tyr Glu Lys Asp Gly
        55                  60                  65

cag ctc ttc tgc aag aag gac tac tgg gcc cgc tat ggc gag tcc tgc      417
Gln Leu Phe Cys Lys Lys Asp Tyr Trp Ala Arg Tyr Gly Glu Ser Cys
    70                  75                  80

cat ggg tgc tct gag caa atc acc aag gga ctg gtt atg gtg gct ggg      465
His Gly Cys Ser Glu Gln Ile Thr Lys Gly Leu Val Met Val Ala Gly
85                  90                  95                  100

gag ctg aag tac cac ccc gag tgt ttc atc tgc ctc acg tgt ggg acc      513
Glu Leu Lys Tyr His Pro Glu Cys Phe Ile Cys Leu Thr Cys Gly Thr
                105                 110                 115

ttt atc ggt gac ggg gac acc tac acg ctg gtg gag cac tcc aag ctg      561
Phe Ile Gly Asp Gly Asp Thr Tyr Thr Leu Val Glu His Ser Lys Leu
            120                 125                 130

tac tgc ggg cac tgc tac tac cag act gtg gtg acc ccc gtc atc gag      609
Tyr Cys Gly His Cys Tyr Tyr Gln Thr Val Val Thr Pro Val Ile Glu
        135                 140                 145
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cag atc ctg cct gac tcc cct ggc tcc cac ctg ccc cac acc gtc acc      657
Gln Ile Leu Pro Asp Ser Pro Gly Ser His Leu Pro His Thr Val Thr
    150                 155                 160

ctg gtg tcc atc cca gcc tca tct cat ggc aag cgt gga ctt tca gtc      705
Leu Val Ser Ile Pro Ala Ser Ser His Gly Lys Arg Gly Leu Ser Val
165                 170                 175                 180

tcc att gac ccc ccg cac ggc cca ccg ggc tgt ggc acc gag cac tca      753
Ser Ile Asp Pro Pro His Gly Pro Pro Gly Cys Gly Thr Glu His Ser
                185                 190                 195

cac acc gtc cgc gtc cag gga gtg gat ccg ggc tgc atg agc cca gat      801
His Thr Val Arg Val Gln Gly Val Asp Pro Gly Cys Met Ser Pro Asp
            200                 205                 210

gtg aag aat tcc atc cac gtc gga gac cgg atc ttg gaa atc aat ggc      849
Val Lys Asn Ser Ile His Val Gly Asp Arg Ile Leu Glu Ile Asn Gly
        215                 220                 225

acg ccc atc cga aat gtg ccc ctg gac gag att gac ctg ctg att cag      897
Thr Pro Ile Arg Asn Val Pro Leu Asp Glu Ile Asp Leu Leu Ile Gln
    230                 235                 240

gaa acc agc cgc ctg ctc cag ctg acc ctc gag cat gac cct cac gat      945
Glu Thr Ser Arg Leu Leu Gln Leu Thr Leu Glu His Asp Pro His Asp
245                 250                 255                 260

aca ctg ggc cac ggg ctg ggg cct gag acc agc ccc ctg agc tct ccg      993
Thr Leu Gly His Gly Leu Gly Pro Glu Thr Ser Pro Leu Ser Ser Pro
                265                 270                 275

gct tat act ccc agc ggg gag gcg ggc agc tct gcc cgg cag aaa cct     1041
Ala Tyr Thr Pro Ser Gly Glu Ala Gly Ser Ser Ala Arg Gln Lys Pro
            280                 285                 290

gtc ttg agg agc tgc agc atc gac agg tct ccg ggc gct ggc tca ctg     1089
Val Leu Arg Ser Cys Ser Ile Asp Arg Ser Pro Gly Ala Gly Ser Leu
        295                 300                 305

ggc tcc ccg gcc tcc cag cgc aag gac ctg ggt cgc tct gag tcc ctc     1137
Gly Ser Pro Ala Ser Gln Arg Lys Asp Leu Gly Arg Ser Glu Ser Leu
    310                 315                 320

cgc gta gtc tgc cgg cca cac cgc atc ttc cgg ccg tcg gac ctc atc     1185
Arg Val Val Cys Arg Pro His Arg Ile Phe Arg Pro Ser Asp Leu Ile
325                 330                 335                 340

cac ggg gag gtg ctg ggc aag ggc tgc ttc ggc cag gct atc aag gtg     1233
His Gly Glu Val Leu Gly Lys Gly Cys Phe Gly Gln Ala Ile Lys Val
                345                 350                 355

aca cac cgt gag aca ggt gag gtg atg gtg atg aag gag ctg atc cgg     1281
Thr His Arg Glu Thr Gly Glu Val Met Val Met Lys Glu Leu Ile Arg
            360                 365                 370

ttc gac gag gag acc cag agg acg ttc ctc aag gag gtg aag gtc atg     1329
Phe Asp Glu Glu Thr Gln Arg Thr Phe Leu Lys Glu Val Lys Val Met
        375                 380                 385

cga tgc ctg gaa cac ccc aac gtg ctc aag ttc atc ggg gtg ctc tac     1377
Arg Cys Leu Glu His Pro Asn Val Leu Lys Phe Ile Gly Val Leu Tyr
    390                 395                 400

aag gac aag agg ctc aac ttc atc act gag tac atc aag ggc ggc acg     1425
Lys Asp Lys Arg Leu Asn Phe Ile Thr Glu Tyr Ile Lys Gly Gly Thr
405                 410                 415                 420

ctc cgg ggc atc atc aag agc atg gac agc cag tac cca tgg agc cag     1473
Leu Arg Gly Ile Ile Lys Ser Met Asp Ser Gln Tyr Pro Trp Ser Gln
                425                 430                 435

aga gtg agc ttt gcc aag gac atc gca tca ggg atg gcc tac ctc cac     1521
Arg Val Ser Phe Ala Lys Asp Ile Ala Ser Gly Met Ala Tyr Leu His
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          440                 445                 450

tcc atg aac atc atc cac cga gac ctc aac tcc cac aac tgc ctg gtc     1569
Ser Met Asn Ile Ile His Arg Asp Leu Asn Ser His Asn Cys Leu Val
       455                 460                 465

cgc gag aac aag aat gtg gtg gtg gct gac ttc ggg ctg gcg cgt ctc     1617
Arg Glu Asn Lys Asn Val Val Val Ala Asp Phe Gly Leu Ala Arg Leu
   470                 475                 480

atg gtg gac gag aag act cag cct gag ggc ctg cgg agc ctc aag aag     1665
Met Val Asp Glu Lys Thr Gln Pro Glu Gly Leu Arg Ser Leu Lys Lys
485                 490                 495                 500

cca gac cgc aag aag cgc tac acc gtg gtg ggc aac ccc tac tgg atg     1713
Pro Asp Arg Lys Lys Arg Tyr Thr Val Val Gly Asn Pro Tyr Trp Met
               505                 510                 515

gca cct gag atg atc aac ggc cgc agc tat gat gag aag gtg gat gtg     1761
Ala Pro Glu Met Ile Asn Gly Arg Ser Tyr Asp Glu Lys Val Asp Val
           520                 525                 530

ttc tcc ttt ggg atc gtc ctg tgc gag atc atc ggg cgg gtg aac gca     1809
Phe Ser Phe Gly Ile Val Leu Cys Glu Ile Ile Gly Arg Val Asn Ala
       535                 540                 545

gac cct gac tac ctg ccc cgc acc atg gac ttt ggc ctc aac gtg cga     1857
Asp Pro Asp Tyr Leu Pro Arg Thr Met Asp Phe Gly Leu Asn Val Arg
   550                 555                 560

gga ttc ctg gac cgc tac tgc ccc cca aac tgc ccc ccg agc ttc ttc     1905
Gly Phe Leu Asp Arg Tyr Cys Pro Pro Asn Cys Pro Pro Ser Phe Phe
565                 570                 575                 580

ccc atc acc gtg cgc tgt tgc gat ctg gac ccc gag aag agg cca tcc     1953
Pro Ile Thr Val Arg Cys Cys Asp Leu Asp Pro Glu Lys Arg Pro Ser
               585                 590                 595

ttt gtg aag ctg gaa cac tgg ctg gag acc ctc cgc atg cac ctg gcc     2001
Phe Val Lys Leu Glu His Trp Leu Glu Thr Leu Arg Met His Leu Ala
           600                 605                 610

ggc cac ctg cca ctg ggc cca cag ctg gag cag ctg gac aga ggt ttc     2049
Gly His Leu Pro Leu Gly Pro Gln Leu Glu Gln Leu Asp Arg Gly Phe
       615                 620                 625

tgg gag acc tac cgg cgc ggc gag agc gga ctg cct gcc cac cct gag     2097
Trp Glu Thr Tyr Arg Arg Gly Glu Ser Gly Leu Pro Ala His Pro Glu
   630                 635                 640

gtc ccc gac tgagccaggg ccactcagct gcccctgtcc ccacctctgg             2146
Val Pro Asp
645

agaatccacc cccaccagat tcctccgcgg gaggtggccc tcagctggga cagtggggac   2206

ccaggcttct cctcagagcc aggccctgac ttgccttctc ccaccccgtg gaccgcttcc   2266

cctgccttct ctctgccgtg gcccagagcc ggcccagctg cacacacaca ccatgctctc   2326

gccctgctgt aacctctgtc ttggcagggc tgtcccctct tgcttctcct tgcatgagct   2386

ggagggcctg tgtgagttac gcccctttcc acacgccgct gccccagcaa ccctgttcac   2446

gctccacctg tctggtccat agctccctgg aggctgggcc aggaggcagc ctccgaacca   2506

tgccccatat aacgcttggg tgcgtgggag ggcgcacatc agggcagagg ccaagttcca   2566

ggtgtctgtg ttcccaggaa ccaaatgggg agtctggggc ccgttttccc cccaggggct   2626

gtctaggtag caacaggtat cgaggactct ccaaaccccc aaagcagaga gagggctgat   2686

cccatggggc ggaggtcccc agtggctgag caaacagccc cttctctcgc tttgggtctt   2746

ttttttgttt ctttcttaaa gccactttag tgagaagcag gtaccaagcc tcagggtgaa   2806
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gggggtccct tgagggagcg tggagctgcg gtgccctggc cggcgatggg gaggagccgg 2866

ctccggcagt gagaggatag gcacagtgga ccgggcaggt gtccaccagc agctcagccc 2926

ctgcagtcat ctcagagccc cttcccgggc ctctccccca aggctccctg ccctcctca 2986

tgcccctctg tcctctgcgt tttttctgtg taatctattt tttaagaaga gtttgtatta 3046

ttttttcata cggctgcagc agcagctgcc aggggcttgg gattttattt ttgtggcggg 3106

cgggggtggg agggccattt tgtcactttg cctcagttga gcatctagga agtattaaaa 3166

ctgtgaagct ttctcagtgc actttgaacc tggaaaacaa tcccaacagg cccgtgggac 3226

catgacttag ggaggtggga cccacccacc cccatccagg aaccgtgacg tccaaggaac 3286

caaacccaga cgcagaacaa taaaataaat tccgtactcc ccaccc 3332

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<213> Homo sapiens

<400> 8

Met Arg Leu Thr Leu Leu Cys Cys Thr Trp Arg Glu Glu Arg Met Gly
1 5 10 15

Glu Glu Gly Ser Glu Leu Pro Val Cys Ala Ser Cys Gly Gln Arg Ile
20 25 30

Tyr Asp Gly Gln Tyr Leu Gln Ala Leu Asn Ala Asp Trp His Ala Asp
35 40 45

Cys Phe Arg Cys Cys Asp Cys Ser Ala Ser Leu Ser His Gln Tyr Tyr
50 55 60

Glu Lys Asp Gly Gln Leu Phe Cys Lys Lys Asp Tyr Trp Ala Arg Tyr
65 70 75 80

Gly Glu Ser Cys His Gly Cys Ser Glu Gln Ile Thr Lys Gly Leu Val
85 90 95

Met Val Ala Gly Glu Leu Lys Tyr His Pro Glu Cys Phe Ile Cys Leu
100 105 110

Thr Cys Gly Thr Phe Ile Gly Asp Gly Asp Thr Tyr Thr Leu Val Glu
115 120 125

His Ser Lys Leu Tyr Cys Gly His Cys Tyr Tyr Gln Thr Val Val Thr
130 135 140

Pro Val Ile Glu Gln Ile Leu Pro Asp Ser Pro Gly Ser His Leu Pro
145 150 155 160

His Thr Val Thr Leu Val Ser Ile Pro Ala Ser Ser His Gly Lys Arg
165 170 175

Gly Leu Ser Val Ser Ile Asp Pro Pro His Gly Pro Pro Gly Cys Gly
180 185 190

Thr Glu His Ser His Thr Val Arg Val Gln Gly Val Asp Pro Gly Cys
195 200 205

Met Ser Pro Asp Val Lys Asn Ser Ile His Val Gly Asp Arg Ile Leu
210 215 220

Glu Ile Asn Gly Thr Pro Ile Arg Asn Val Pro Leu Asp Glu Ile Asp
225 230 235 240

Leu Leu Ile Gln Glu Thr Ser Arg Leu Leu Gln Leu Thr Leu Glu His
245 250 255

Asp Pro His Asp Thr Leu Gly His Gly Leu Gly Pro Glu Thr Ser Pro
260 265 270

Leu Ser Ser Pro Ala Tyr Thr Pro Ser Gly Glu Ala Gly Ser Ser Ala
275 280 285

Arg Gln Lys Pro Val Leu Arg Ser Cys Ser Ile Asp Arg Ser Pro Gly
290 295 300

Ala Gly Ser Leu Gly Ser Pro Ala Ser Gln Arg Lys Asp Leu Gly Arg
305 310 315 320

Ser Glu Ser Leu Arg Val Val Cys Arg Pro His Arg Ile Phe Arg Pro
325 330 335

Ser Asp Leu Ile His Gly Glu Val Leu Gly Lys Gly Cys Phe Gly Gln
340 345 350

Ala Ile Lys Val Thr His Arg Glu Thr Gly Glu Val Met Val Met Lys
355 360 365

Glu Leu Ile Arg Phe Asp Glu Glu Thr Gln Arg Thr Phe Leu Lys Glu
370 375 380

Val Lys Val Met Arg Cys Leu Glu His Pro Asn Val Leu Lys Phe Ile
385 390 395 400

Gly Val Leu Tyr Lys Asp Lys Arg Leu Asn Phe Ile Thr Glu Tyr Ile
405 410 415

Lys Gly Gly Thr Leu Arg Gly Ile Ile Lys Ser Met Asp Ser Gln Tyr
420 425 430

Pro Trp Ser Gln Arg Val Ser Phe Ala Lys Asp Ile Ala Ser Gly Met
435 440 445

Ala Tyr Leu His Ser Met Asn Ile Ile His Arg Asp Leu Asn Ser His
450 455 460

Asn Cys Leu Val Arg Glu Asn Lys Asn Val Val Val Ala Asp Phe Gly
465 470 475 480

Leu Ala Arg Leu Met Val Asp Glu Lys Thr Gln Pro Glu Gly Leu Arg
485 490 495

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Ser Leu Lys Lys Pro Asp Arg Lys Lys Arg Tyr Thr Val Val Gly Asn
            500                 505                 510

Pro Tyr Trp Met Ala Pro Glu Met Ile Asn Gly Arg Ser Tyr Asp Glu
        515                 520                 525

Lys Val Asp Val Phe Ser Phe Gly Ile Val Leu Cys Glu Ile Ile Gly
    530                 535                 540

Arg Val Asn Ala Asp Pro Asp Tyr Leu Pro Arg Thr Met Asp Phe Gly
545                 550                 555                 560

Leu Asn Val Arg Gly Phe Leu Asp Arg Tyr Cys Pro Pro Asn Cys Pro
                565                 570                 575

Pro Ser Phe Phe Pro Ile Thr Val Arg Cys Cys Asp Leu Asp Pro Glu
            580                 585                 590

Lys Arg Pro Ser Phe Val Lys Leu Glu His Trp Leu Glu Thr Leu Arg
        595                 600                 605

Met His Leu Ala Gly His Leu Pro Leu Gly Pro Gln Leu Glu Gln Leu
    610                 615                 620

Asp Arg Gly Phe Trp Glu Thr Tyr Arg Arg Gly Glu Ser Gly Leu Pro
625                 630                 635                 640

Ala His Pro Glu Val Pro Asp
                645
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<211> 3701
<212> DNA
<213> Homo sapiens

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<222> (146)..(2059)

<400> 9

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gcaggagctg aggggagttg tagggaactg aggggagctg ctgtgtcccc cgcctcctcc    120

tccccatttc cgcgctcccg ggacc atg tcc gcg ctg gcg ggt gaa gat gtc       172
                              Met Ser Ala Leu Ala Gly Glu Asp Val
                              1               5

tgg agg tgt cca ggc tgt ggg gac cac att gct cca agc cag ata tgg       220
Trp Arg Cys Pro Gly Cys Gly Asp His Ile Ala Pro Ser Gln Ile Trp
10                  15                  20                  25

tac agg act gtc aac gaa acc tgg cac ggc tct tgc ttc cgg tgt tca       268
Tyr Arg Thr Val Asn Glu Thr Trp His Gly Ser Cys Phe Arg Cys Ser
                30                  35                  40

gaa tgc cag gat tcc ctc acc aac tgg tac tat gag aag gat ggg aag       316
Glu Cys Gln Asp Ser Leu Thr Asn Trp Tyr Tyr Glu Lys Asp Gly Lys
            45                  50                  55

ctc tac tgc ccc aag gac tac tgg ggg aag ttt ggg gag ttc tgt cat       364
Leu Tyr Cys Pro Lys Asp Tyr Trp Gly Lys Phe Gly Glu Phe Cys His
        60                  65                  70
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ggg tgc tcc ctg ctg atg aca ggg cct ttt atg gtg gct ggg gag ttc      412
Gly Cys Ser Leu Leu Met Thr Gly Pro Phe Met Val Ala Gly Glu Phe
    75                  80                  85

aag tac cac cca gag tgc ttt gcc tgt atg agc tgc aag gtg atc att      460
Lys Tyr His Pro Glu Cys Phe Ala Cys Met Ser Cys Lys Val Ile Ile
90                  95                  100                 105

gag gat ggg gat gca tat gca ctg gtg cag cat gcc acc ctc tac tgt      508
Glu Asp Gly Asp Ala Tyr Ala Leu Val Gln His Ala Thr Leu Tyr Cys
                110                 115                 120

ggg aag tgc cac aat gag gtg gtg ctg gca ccc atg ttt gag aga ctc      556
Gly Lys Cys His Asn Glu Val Val Leu Ala Pro Met Phe Glu Arg Leu
            125                 130                 135

tcc aca gag tct gtt cag gag cag ctg ccc tac tct gtc acg ctc atc      604
Ser Thr Glu Ser Val Gln Glu Gln Leu Pro Tyr Ser Val Thr Leu Ile
        140                 145                 150

tcc atg ccg gcc acc act gaa ggc agg cgg ggc ttc tcc gtg tcc gtg      652
Ser Met Pro Ala Thr Thr Glu Gly Arg Arg Gly Phe Ser Val Ser Val
    155                 160                 165

gag agt gcc tgc tcc aac tac gcc acc act gtg caa gtg aaa gag gtc      700
Glu Ser Ala Cys Ser Asn Tyr Ala Thr Thr Val Gln Val Lys Glu Val
170                 175                 180                 185

aac cgg atg cac atc agt ccc aac aat cga aac gcc atc cac cct ggg      748
Asn Arg Met His Ile Ser Pro Asn Asn Arg Asn Ala Ile His Pro Gly
                190                 195                 200

gac cgc atc ctg gag atc aat ggg acc ccc gtc cgc aca ctt cga gtg      796
Asp Arg Ile Leu Glu Ile Asn Gly Thr Pro Val Arg Thr Leu Arg Val
            205                 210                 215

gag gag gtg gag gat gca att agc cag acg agc cag aca ctt cag ctg      844
Glu Glu Val Glu Asp Ala Ile Ser Gln Thr Ser Gln Thr Leu Gln Leu
        220                 225                 230

ttg att gaa cat gac ccc gtc tcc caa cgc ctg gac cag ctg cgg ctg      892
Leu Ile Glu His Asp Pro Val Ser Gln Arg Leu Asp Gln Leu Arg Leu
    235                 240                 245

gag gcc cgg ctc gct cct cac atg cag aat gcc gga cac ccc cac gcc      940
Glu Ala Arg Leu Ala Pro His Met Gln Asn Ala Gly His Pro His Ala
250                 255                 260                 265

ctc agc acc ctg gac acc aag gag aat ctg gag ggg aca ctg agg aga      988
Leu Ser Thr Leu Asp Thr Lys Glu Asn Leu Glu Gly Thr Leu Arg Arg
                270                 275                 280

cgt tcc cta agg cgc agt aac agt atc tcc aag tcc cct ggc ccc agc     1036
Arg Ser Leu Arg Arg Ser Asn Ser Ile Ser Lys Ser Pro Gly Pro Ser
            285                 290                 295

tcc cca aag gag ccc ctg ctg ttc agc cgt gac atc agc cgc tca gaa     1084
Ser Pro Lys Glu Pro Leu Leu Phe Ser Arg Asp Ile Ser Arg Ser Glu
        300                 305                 310

tcc ctt cgt tgt tcc agc agc tat tca cag cag atc ttc cgg ccc tgt     1132
Ser Leu Arg Cys Ser Ser Ser Tyr Ser Gln Gln Ile Phe Arg Pro Cys
    315                 320                 325

gac cta atc cat ggg gag gtc ctg ggg aag ggc ttc ttt ggg cag gct     1180
Asp Leu Ile His Gly Glu Val Leu Gly Lys Gly Phe Phe Gly Gln Ala
330                 335                 340                 345

atc aag gtg aca cac aaa gcc acg ggc aaa gtg atg gtc atg aaa gag     1228
Ile Lys Val Thr His Lys Ala Thr Gly Lys Val Met Val Met Lys Glu
                350                 355                 360

tta att cga tgt gat gag gag acc cag aaa act ttt ctg act gag gtg     1276
Leu Ile Arg Cys Asp Glu Glu Thr Gln Lys Thr Phe Leu Thr Glu Val
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            365                 370                 375

aaa gtg atg cgc agc ctg gac cac ccc aat gtg ctc aag ttc att ggt     1324
Lys Val Met Arg Ser Leu Asp His Pro Asn Val Leu Lys Phe Ile Gly
        380                 385                 390

gtg ctg tac aag gat aag aag ctg aac ctc ctg aca gag tac att gag     1372
Val Leu Tyr Lys Asp Lys Lys Leu Asn Leu Leu Thr Glu Tyr Ile Glu
    395                 400                 405

ggg ggc aca ctg aag gac ttt ctg cgc agt atg gat ccg ttc ccc tgg     1420
Gly Gly Thr Leu Lys Asp Phe Leu Arg Ser Met Asp Pro Phe Pro Trp
410                 415                 420                 425

cag cag aag gtc agg ttt gcc aaa gga atc gcc tcc gga atg gcc tat     1468
Gln Gln Lys Val Arg Phe Ala Lys Gly Ile Ala Ser Gly Met Ala Tyr
                430                 435                 440

ttg cac tct atg tgc atc atc cac cgg gat ctg aac tcg cac aac tgc     1516
Leu His Ser Met Cys Ile Ile His Arg Asp Leu Asn Ser His Asn Cys
            445                 450                 455

ctc atc aag ttg gac aag act gtg gtg gtg gca gac ttt ggg ctg tca     1564
Leu Ile Lys Leu Asp Lys Thr Val Val Val Ala Asp Phe Gly Leu Ser
        460                 465                 470

cgg ctc ata gtg gaa gag agg aaa agg gcc ccc atg gag aag gcc acc     1612
Arg Leu Ile Val Glu Glu Arg Lys Arg Ala Pro Met Glu Lys Ala Thr
    475                 480                 485

acc aag aaa cgc acc ttg cgc aag aac gac cgc aag aag cgc tac acg     1660
Thr Lys Lys Arg Thr Leu Arg Lys Asn Asp Arg Lys Lys Arg Tyr Thr
490                 495                 500                 505

gtg gtg gga aac ccc tac tgg atg gcc cct gag atg ctg aac gga aag     1708
Val Val Gly Asn Pro Tyr Trp Met Ala Pro Glu Met Leu Asn Gly Lys
                510                 515                 520

agc tat gat gag acg gtg gat atc ttc tcc ttt ggg atc gtt ctc tgt     1756
Ser Tyr Asp Glu Thr Val Asp Ile Phe Ser Phe Gly Ile Val Leu Cys
            525                 530                 535

gag atc att ggg cag gtg tat gca gat cct gac tgc ctt ccc cga aca     1804
Glu Ile Ile Gly Gln Val Tyr Ala Asp Pro Asp Cys Leu Pro Arg Thr
        540                 545                 550

ctg gac ttt ggc ctc aac gtg aag ctt ttc tgg gag aag ttt gtt ccc     1852
Leu Asp Phe Gly Leu Asn Val Lys Leu Phe Trp Glu Lys Phe Val Pro
    555                 560                 565

aca gat tgt ccc ccg gcc ttc ttc ccg ctg gcc gcc atc tgc tgc aga     1900
Thr Asp Cys Pro Pro Ala Phe Phe Pro Leu Ala Ala Ile Cys Cys Arg
570                 575                 580                 585

ctg gag cct gag agc aga cca gca ttc tcg aaa ttg gag gac tcc ttt     1948
Leu Glu Pro Glu Ser Arg Pro Ala Phe Ser Lys Leu Glu Asp Ser Phe
                590                 595                 600

gag gcc ctc tcc ctg tac ctg ggg gag ctg ggc atc ccg ctg cct gca     1996
Glu Ala Leu Ser Leu Tyr Leu Gly Glu Leu Gly Ile Pro Leu Pro Ala
            605                 610                 615

gag ctg gag gag ttg gac cac act gtg agc atg cag tac ggc ctg acc     2044
Glu Leu Glu Glu Leu Asp His Thr Val Ser Met Gln Tyr Gly Leu Thr
        620                 625                 630

cgg gac tca cct ccc tagccctggc ccagcccccc gcaggggggt gttctacagc     2099
Arg Asp Ser Pro Pro
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gcaagcttgc tttagggctg agccctggac tcccagcagc agcacagttc agcattgtgt 3599

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35 40 45

Asn Trp Tyr Tyr Glu Lys Asp Gly Lys Leu Tyr Cys Pro Lys Asp Tyr
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Trp Gly Lys Phe Gly Glu Phe Cys His Gly Cys Ser Leu Leu Met Thr
65 70 75 80

Gly Pro Phe Met Val Ala Gly Glu Phe Lys Tyr His Pro Glu Cys Phe
85 90 95

Ala Cys Met Ser Cys Lys Val Ile Ile Glu Asp Gly Asp Ala Tyr Ala
100 105 110

Leu Val Gln His Ala Thr Leu Tyr Cys Gly Lys Cys His Asn Glu Val
115 120 125

Val Leu Ala Pro Met Phe Glu Arg Leu Ser Thr Glu Ser Val Gln Glu
130 135 140

Gln Leu Pro Tyr Ser Val Thr Leu Ile Ser Met Pro Ala Thr Thr Glu
145 150 155 160

Gly Arg Arg Gly Phe Ser Val Ser Val Glu Ser Ala Cys Ser Asn Tyr
165 170 175

Ala Thr Thr Val Gln Val Lys Glu Val Asn Arg Met His Ile Ser Pro
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Asn Asn Arg Asn Ala Ile His Pro Gly Asp Arg Ile Leu Glu Ile Asn
195 200 205

Gly Thr Pro Val Arg Thr Leu Arg Val Glu Glu Val Glu Asp Ala Ile
210 215 220

Ser Gln Thr Ser Gln Thr Leu Gln Leu Leu Ile Glu His Asp Pro Val
225 230 235 240

Ser Gln Arg Leu Asp Gln Leu Arg Leu Glu Ala Arg Leu Ala Pro His
245 250 255

Met Gln Asn Ala Gly His Pro His Ala Leu Ser Thr Leu Asp Thr Lys
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Glu Asn Leu Glu Gly Thr Leu Arg Arg Arg Ser Leu Arg Arg Ser Asn
275 280 285

Ser Ile Ser Lys Ser Pro Gly Pro Ser Ser Pro Lys Glu Pro Leu Leu
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Phe Ser Arg Asp Ile Ser Arg Ser Glu Ser Leu Arg Cys Ser Ser Ser
305 310 315 320

Tyr Ser Gln Gln Ile Phe Arg Pro Cys Asp Leu Ile His Gly Glu Val
325 330 335

Leu Gly Lys Gly Phe Phe Gly Gln Ala Ile Lys Val Thr His Lys Ala
340 345 350

Thr Gly Lys Val Met Val Met Lys Glu Leu Ile Arg Cys Asp Glu Glu
355 360 365

Thr Gln Lys Thr Phe Leu Thr Glu Val Lys Val Met Arg Ser Leu Asp

370 375 380

His Pro Asn Val Leu Lys Phe Ile Gly Val Leu Tyr Lys Asp Lys Lys
385 390 395 400

Leu Asn Leu Leu Thr Glu Tyr Ile Glu Gly Gly Thr Leu Lys Asp Phe
405 410 415

Leu Arg Ser Met Asp Pro Phe Pro Trp Gln Gln Lys Val Arg Phe Ala
420 425 430

Lys Gly Ile Ala Ser Gly Met Ala Tyr Leu His Ser Met Cys Ile Ile
435 440 445

His Arg Asp Leu Asn Ser His Asn Cys Leu Ile Lys Leu Asp Lys Thr
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Val Val Val Ala Asp Phe Gly Leu Ser Arg Leu Ile Val Glu Glu Arg
465 470 475 480

Lys Arg Ala Pro Met Glu Lys Ala Thr Thr Lys Lys Arg Thr Leu Arg
485 490 495

Lys Asn Asp Arg Lys Lys Arg Tyr Thr Val Val Gly Asn Pro Tyr Trp
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Met Ala Pro Glu Met Leu Asn Gly Lys Ser Tyr Asp Glu Thr Val Asp
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Ile Phe Ser Phe Gly Ile Val Leu Cys Glu Ile Ile Gly Gln Val Tyr
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Ala Asp Pro Asp Cys Leu Pro Arg Thr Leu Asp Phe Gly Leu Asn Val
545 550 555 560

Lys Leu Phe Trp Glu Lys Phe Val Pro Thr Asp Cys Pro Pro Ala Phe
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Phe Pro Leu Ala Ala Ile Cys Cys Arg Leu Glu Pro Glu Ser Arg Pro
580 585 590

Ala Phe Ser Lys Leu Glu Asp Ser Phe Glu Ala Leu Ser Leu Tyr Leu
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ctggtcttca gctacccgcc ttcgtctccg agtttgcgac tcgcggaccg gcgtccccgg 240

cgcgaagagg ctggactcgg attcgttgcc tgagca atg gct gcc atc cgg aag 294
Met Ala Ala Ile Arg Lys
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Lys Leu Val Ile Val Gly Asp Gly Ala Cys Gly Lys Thr Cys Leu Leu
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Ile Val Phe Ser Lys Asp Gln Phe Pro Glu Val Tyr Val Pro Thr Val
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ttt gag aac tat gtg gca gat atc gag gtg gat gga aag cag gta gag 438
Phe Glu Asn Tyr Val Ala Asp Ile Glu Val Asp Gly Lys Gln Val Glu
40 45 50

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Leu Ala Leu Trp Asp Thr Ala Gly Gln Glu Asp Tyr Asp Arg Leu Arg
55 60 65 70

ccc ctc tcc tac cca gat acc gat gtt ata ctg atg tgt ttt tcc atc 534
Pro Leu Ser Tyr Pro Asp Thr Asp Val Ile Leu Met Cys Phe Ser Ile
75 80 85

gac agc cct gat agt tta gaa aac atc cca gaa aag tgg acc cca gaa 582
Asp Ser Pro Asp Ser Leu Glu Asn Ile Pro Glu Lys Trp Thr Pro Glu
90 95 100

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Val Lys His Phe Cys Pro Asn Val Pro Ile Ile Leu Val Gly Asn Lys
105 110 115

aag gat ctt cgg aat gat gag cac aca agg cgg gag cta gcc aag atg 678
Lys Asp Leu Arg Asn Asp Glu His Thr Arg Arg Glu Leu Ala Lys Met
120 125 130

aag cag gag ccg gtg aaa cct gaa gaa ggc aga gat atg gca aac agg 726
Lys Gln Glu Pro Val Lys Pro Glu Glu Gly Arg Asp Met Ala Asn Arg
135 140 145 150

att ggc gct ttt ggg tac atg gag tgt tca gca aag acc aaa gat gga 774
Ile Gly Ala Phe Gly Tyr Met Glu Cys Ser Ala Lys Thr Lys Asp Gly
155 160 165

gtg aga gag gtt ttt gaa atg gct acg aga gct gct ctg caa gct aga 822
Val Arg Glu Val Phe Glu Met Ala Thr Arg Ala Ala Leu Gln Ala Arg
170 175 180

cgt ggg aag aaa aaa tct ggg tgc ctt gtc ttg tga aaccttgctg 868
Arg Gly Lys Lys Lys Ser Gly Cys Leu Val Leu
185 190

caagcacagc ccttatgcgg ttaattttga agtgctgttt attaatctta gtgtatgatt 928

actggccttt ttcatttatc tataatttac ctaagattac aaatcagaag tcatcttgct 988

accagtattt agaagccaac tatgattatt aacgatgtcc aacccgtctg gcccaccagg 1048

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35 40 45

Asp Gly Lys Gln Val Glu Leu Ala Leu Trp Asp Thr Ala Gly Gln Glu
50 55 60

Asp Tyr Asp Arg Leu Arg Pro Leu Ser Tyr Pro Asp Thr Asp Val Ile
65 70 75 80

Leu Met Cys Phe Ser Ile Asp Ser Pro Asp Ser Leu Glu Asn Ile Pro
85 90 95

Glu Lys Trp Thr Pro Glu Val Lys His Phe Cys Pro Asn Val Pro Ile
100 105 110

Ile Leu Val Gly Asn Lys Lys Asp Leu Arg Asn Asp Glu His Thr Arg
115 120 125

Arg Glu Leu Ala Lys Met Lys Gln Glu Pro Val Lys Pro Glu Glu Gly
130 135 140

Arg Asp Met Ala Asn Arg Ile Gly Ala Phe Gly Tyr Met Glu Cys Ser
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Leu

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Met Ser Thr Gly Asp
1 5

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Ser Phe Glu Thr Arg Phe Glu Lys Met Asp Asn Leu Leu Arg Asp Pro
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Lys Ser Glu Val Asn Ser Asp Cys Leu Leu Asp Gly Leu Asp Ala Leu
25 30 35

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Val Tyr Asp Leu Asp Phe Pro Ala Leu Arg Lys Asn Lys Asn Ile Asp
40 45 50

aac ttt tta agc aga tat aaa gac aca ata aat aaa atc aga gat tta 1148
Asn Phe Leu Ser Arg Tyr Lys Asp Thr Ile Asn Lys Ile Arg Asp Leu
55 60 65

cga atg aaa gct gaa gat tat gaa gta gtg aag gtg att ggt aga ggt 1196
Arg Met Lys Ala Glu Asp Tyr Glu Val Val Lys Val Ile Gly Arg Gly
70 75 80 85

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Ala Phe Gly Glu Val Gln Leu Val Arg His Lys Ser Thr Arg Lys Val
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tat gct atg aag ctt ctc agc aaa ttt gaa atg ata aag aga tct gat     1292
Tyr Ala Met Lys Leu Leu Ser Lys Phe Glu Met Ile Lys Arg Ser Asp
            105                 110                 115

tct gct ttt ttc tgg gaa gaa agg gac atc atg gct ttt gcc aac agt     1340
Ser Ala Phe Phe Trp Glu Glu Arg Asp Ile Met Ala Phe Ala Asn Ser
        120                 125                 130

cct tgg gtt gtt cag ctt ttt tat gca ttc caa gat gat cgt tat ctc     1388
Pro Trp Val Val Gln Leu Phe Tyr Ala Phe Gln Asp Asp Arg Tyr Leu
    135                 140                 145

tac atg gtg atg gaa tac atg cct ggt gga gat ctt gta aac tta atg     1436
Tyr Met Val Met Glu Tyr Met Pro Gly Gly Asp Leu Val Asn Leu Met
150                 155                 160                 165

agc aac tat gat gtg cct gaa aaa tgg gca cga ttc tat act gca gaa     1484
Ser Asn Tyr Asp Val Pro Glu Lys Trp Ala Arg Phe Tyr Thr Ala Glu
                170                 175                 180

gta gtt ctt gca ttg gat gca atc cat tcc atg ggt ttt att cac aga     1532
Val Val Leu Ala Leu Asp Ala Ile His Ser Met Gly Phe Ile His Arg
            185                 190                 195

gat gtg aag cct gat aac atg ctg ctg gat aaa tct gga cat ttg aag     1580
Asp Val Lys Pro Asp Asn Met Leu Leu Asp Lys Ser Gly His Leu Lys
        200                 205                 210

tta gca gat ttt ggt act tgt atg aag atg aat aag gaa ggc atg gta     1628
Leu Ala Asp Phe Gly Thr Cys Met Lys Met Asn Lys Glu Gly Met Val
    215                 220                 225

cga tgt gat aca gcg gtt gga aca cct gat tat att tcc cct gaa gta     1676
Arg Cys Asp Thr Ala Val Gly Thr Pro Asp Tyr Ile Ser Pro Glu Val
230                 235                 240                 245

tta aaa tcc caa ggt ggt gat ggt tat tat gga aga gaa tgt gac tgg     1724
Leu Lys Ser Gln Gly Gly Asp Gly Tyr Tyr Gly Arg Glu Cys Asp Trp
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Trp Ser Val Gly Val Phe Leu Tyr Glu Met Leu Val Gly Asp Thr Pro
            265                 270                 275

ttt tat gca gat tct ttg gtt gga act tac agt aaa att atg aac cat     1820
Phe Tyr Ala Asp Ser Leu Val Gly Thr Tyr Ser Lys Ile Met Asn His
        280                 285                 290

aaa aat tca ctt acc ttt cct gat gat aat gac ata tca aaa gaa gca     1868
Lys Asn Ser Leu Thr Phe Pro Asp Asp Asn Asp Ile Ser Lys Glu Ala
    295                 300                 305

aaa aac ctt att tgt gcc ttc ctt act gac agg gaa gtg agg tta ggg     1916
Lys Asn Leu Ile Cys Ala Phe Leu Thr Asp Arg Glu Val Arg Leu Gly
310                 315                 320                 325

cga aat ggt gta gaa gaa atc aaa cga cat ctc ttc ttc aaa aat gac     1964
Arg Asn Gly Val Glu Glu Ile Lys Arg His Leu Phe Phe Lys Asn Asp
                330                 335                 340

cag tgg gct tgg gaa acg ctc cga gac act gta gca cca gtt gta ccc     2012
Gln Trp Ala Trp Glu Thr Leu Arg Asp Thr Val Ala Pro Val Val Pro
            345                 350                 355

gat tta agt agt gac att gat act agt aat ttt gat gac ttg gaa gaa     2060
Asp Leu Ser Ser Asp Ile Asp Thr Ser Asn Phe Asp Asp Leu Glu Glu
        360                 365                 370

gat aaa gga gag gaa gaa aca ttc cct att cct aaa gct ttc gtt ggc     2108
Asp Lys Gly Glu Glu Glu Thr Phe Pro Ile Pro Lys Ala Phe Val Gly
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390                 395                 400                 405

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Leu Ser Ser Ala Asn Pro Asn Asp Asn Arg Thr Ser Ser Asn Ala Asp
                410                 415                 420

aaa agc ttg cag gaa agt ttg caa aaa aca atc tat aag ctg gaa gaa     2252
Lys Ser Leu Gln Glu Ser Leu Gln Lys Thr Ile Tyr Lys Leu Glu Glu
            425                 430                 435

cag ctg cat aat gaa atg cag tta aaa gat gaa atg gag cag aag tgc     2300
Gln Leu His Asn Glu Met Gln Leu Lys Asp Glu Met Glu Gln Lys Cys
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aga acc tca aac ata aaa cta gac aag ata atg aaa gaa ttg gat gaa     2348
Arg Thr Ser Asn Ile Lys Leu Asp Lys Ile Met Lys Glu Leu Asp Glu
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Glu Gly Asn Gln Arg Arg Asn Leu Glu Ser Thr Val Ser Gln Ile Glu
470                 475                 480                 485

aag gag aaa atg ttg cta cag cat aga att aat gag tac caa aga aaa     2444
Lys Glu Lys Met Leu Leu Gln His Arg Ile Asn Glu Tyr Gln Arg Lys
                490                 495                 500

gct gaa cag gaa aat gag aag aga aga aat gta gaa aat gaa gtt tct     2492
Ala Glu Gln Glu Asn Glu Lys Arg Arg Asn Val Glu Asn Glu Val Ser
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aca tta aag gat cag ttg gaa gac tta aag aaa gtc agt cag aat tca     2540
Thr Leu Lys Asp Gln Leu Glu Asp Leu Lys Lys Val Ser Gln Asn Ser
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cag ctt gct aat gag aag ctg tcc cag tta caa aag cag cta gaa gaa     2588
Gln Leu Ala Asn Glu Lys Leu Ser Gln Leu Gln Lys Gln Leu Glu Glu
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gcc aat gac tta ctt agg aca gaa tcg gac aca gct gta aga ttg agg     2636
Ala Asn Asp Leu Leu Arg Thr Glu Ser Asp Thr Ala Val Arg Leu Arg
550                 555                 560                 565

aag agt cac aca gag atg agc aag tca att agt cag tta gag tcc ctg     2684
Lys Ser His Thr Glu Met Ser Lys Ser Ile Ser Gln Leu Glu Ser Leu
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aac aga gag ttg caa gag aga aat cga att tta gag aat tct aag tca     2732
Asn Arg Glu Leu Gln Glu Arg Asn Arg Ile Leu Glu Asn Ser Lys Ser
            585                 590                 595

caa aca gac aaa gat tat tac cag ctg caa gct ata tta gaa gct gaa     2780
Gln Thr Asp Lys Asp Tyr Tyr Gln Leu Gln Ala Ile Leu Glu Ala Glu
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cga aga gac aga ggt cat gat tct gag atg att gga gac ctt caa gct     2828
Arg Arg Asp Arg Gly His Asp Ser Glu Met Ile Gly Asp Leu Gln Ala
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cga att aca tct tta caa gag gag gtg aag cat ctc aaa cat aat ctc     2876
Arg Ile Thr Ser Leu Gln Glu Glu Val Lys His Leu Lys His Asn Leu
630                 635                 640                 645

gaa aaa gtg gaa gga gaa aga aaa gag gct caa gac atg ctt aat cac     2924
Glu Lys Val Glu Gly Glu Arg Lys Glu Ala Gln Asp Met Leu Asn His
                650                 655                 660

tca gaa aag gaa aag aat aat tta gag ata gat tta aac tac aaa ctt     2972
Ser Glu Lys Glu Lys Asn Asn Leu Glu Ile Asp Leu Asn Tyr Lys Leu
            665                 670                 675

aaa tca tta caa caa cgg tta gaa caa gag gta aat gaa cac aaa gta     3020
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Lys Ser Leu Gln Gln Arg Leu Glu Gln Glu Val Asn Glu His Lys Val
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acc aaa gct cgt tta act gac aaa cat caa tct att gaa gag gca aag     3068
Thr Lys Ala Arg Leu Thr Asp Lys His Gln Ser Ile Glu Glu Ala Lys
    695                 700                 705

tct gtg gca atg tgt gag atg gaa aaa aag ctg aaa gaa gaa aga gaa     3116
Ser Val Ala Met Cys Glu Met Glu Lys Lys Leu Lys Glu Glu Arg Glu
710                 715                 720                 725

gct cga gag aag gct gaa aat cgg gtt gtt cag att gag aaa cag tgt     3164
Ala Arg Glu Lys Ala Glu Asn Arg Val Val Gln Ile Glu Lys Gln Cys
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tcc atg cta gac gtt gat ctg aag caa tct cag cag aaa cta gaa cat     3212
Ser Met Leu Asp Val Asp Leu Lys Gln Ser Gln Gln Lys Leu Glu His
            745                 750                 755

ttg act gga aat aaa gaa agg atg gag gat gaa gtt aag aat cta acc     3260
Leu Thr Gly Asn Lys Glu Arg Met Glu Asp Glu Val Lys Asn Leu Thr
        760                 765                 770

ctg caa ctg gag cag gaa tca aat aag cgg ctg ttg tta caa aat gaa     3308
Leu Gln Leu Glu Gln Glu Ser Asn Lys Arg Leu Leu Leu Gln Asn Glu
    775                 780                 785

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Leu Lys Thr Gln Ala Phe Glu Ala Asp Asn Leu Lys Gly Leu Glu Lys
790                 795                 800                 805

cag atg aaa cag gaa ata aat act tta ttg gaa gca aag aga tta tta     3404
Gln Met Lys Gln Glu Ile Asn Thr Leu Leu Glu Ala Lys Arg Leu Leu
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gaa ttt gag tta gct cag ctt acg aaa cag tat aga gga aat gaa gga     3452
Glu Phe Glu Leu Ala Gln Leu Thr Lys Gln Tyr Arg Gly Asn Glu Gly
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cag atg cgg gag cta caa gat cag ctt gaa gct gag caa tat ttc tcg     3500
Gln Met Arg Glu Leu Gln Asp Gln Leu Glu Ala Glu Gln Tyr Phe Ser
        840                 845                 850

aca ctt tat aaa acc cag gta aag gaa ctt aaa gaa gaa att gaa gaa     3548
Thr Leu Tyr Lys Thr Gln Val Lys Glu Leu Lys Glu Glu Ile Glu Glu
    855                 860                 865

aaa aac aga gaa aat tta aag aaa ata cag gaa cta caa aat gaa aaa     3596
Lys Asn Arg Glu Asn Leu Lys Lys Ile Gln Glu Leu Gln Asn Glu Lys
870                 875                 880                 885

gaa act ctt gct act cag ttg gat cta gca gaa aca aaa gct gag tct     3644
Glu Thr Leu Ala Thr Gln Leu Asp Leu Ala Glu Thr Lys Ala Glu Ser
                890                 895                 900

gag cag ttg gcg cga ggc ctt ctg gaa gaa cag tat ttt gaa ttg acg     3692
Glu Gln Leu Ala Arg Gly Leu Leu Glu Glu Gln Tyr Phe Glu Leu Thr
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caa gaa agc aag aaa gct gct tca aga aat aga caa gag att aca gat     3740
Gln Glu Ser Lys Lys Ala Ala Ser Arg Asn Arg Gln Glu Ile Thr Asp
        920                 925                 930

aaa gat cac act gtt agt cgg ctt gaa gaa gca aac agc atg cta acc     3788
Lys Asp His Thr Val Ser Arg Leu Glu Glu Ala Asn Ser Met Leu Thr
    935                 940                 945

aaa gat att gaa ata tta aga aga gag aat gaa gag cta aca gag aaa     3836
Lys Asp Ile Glu Ile Leu Arg Arg Glu Asn Glu Glu Leu Thr Glu Lys
950                 955                 960                 965

atg aag aag gca gag gaa gaa tat aaa ctg gag aag gag gag gag atc     3884
Met Lys Lys Ala Glu Glu Glu Tyr Lys Leu Glu Lys Glu Glu Glu Ile
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Ser Asn Leu Lys Ala Ala Phe Glu Lys Asn Ile Asn Thr Glu Arg Thr
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ctt aaa aca  cag gct gtt aac aaa  ttg gca gaa ata atg  aat cga     3977
Leu Lys Thr  Gln Ala Val Asn Lys  Leu Ala Glu Ile Met  Asn Arg
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aaa gat ttt  aaa att gat aga aag  aaa gct aat aca caa  gat ttg     4022
Lys Asp Phe  Lys Ile Asp Arg Lys  Lys Ala Asn Thr Gln  Asp Leu
        1015                1020                1025

aga aag aaa  gaa aag gaa aat cga  aag ctg caa ctg gaa  ctc aac     4067
Arg Lys Lys  Glu Lys Glu Asn Arg  Lys Leu Gln Leu Glu  Leu Asn
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caa gaa aga  gag aaa ttc aac cag  atg gta gtg aaa cat  cag aag     4112
Gln Glu Arg  Glu Lys Phe Asn Gln  Met Val Val Lys His  Gln Lys
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gaa ctg aat  gac atg caa gcg caa  ttg gta gaa gaa tgt  gca cat     4157
Glu Leu Asn  Asp Met Gln Ala Gln  Leu Val Glu Glu Cys  Ala His
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agg aat gag  ctt cag atg cag ttg  gcc agc aaa gag agt  gat att     4202
Arg Asn Glu  Leu Gln Met Gln Leu  Ala Ser Lys Glu Ser  Asp Ile
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gag caa ttg  cgt gct aaa ctt ttg  gac ctc tcg gat tct  aca agt     4247
Glu Gln Leu  Arg Ala Lys Leu Leu  Asp Leu Ser Asp Ser  Thr Ser
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gtt gct agt  ttt cct agt gct gat  gaa act gat ggt aac  ctc cca     4292
Val Ala Ser  Phe Pro Ser Ala Asp  Glu Thr Asp Gly Asn  Leu Pro
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gag tca aga  att gaa ggt tgg ctt  tca gta cca aat aga  gga aat     4337
Glu Ser Arg  Ile Glu Gly Trp Leu  Ser Val Pro Asn Arg  Gly Asn
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atc aaa cga  tat ggc tgg aag aaa  cag tat gtt gtg gta  agc agc     4382
Ile Lys Arg  Tyr Gly Trp Lys Lys  Gln Tyr Val Val Val  Ser Ser
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aaa aaa att  ttg ttc tat aat gac  gaa caa gat aag gag  caa tcc     4427
Lys Lys Ile  Leu Phe Tyr Asn Asp  Glu Gln Asp Lys Glu  Gln Ser
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aat cca tct  atg gta ttg gac ata  gat aaa ctg ttt cac  gtt aga     4472
Asn Pro Ser  Met Val Leu Asp Ile  Asp Lys Leu Phe His  Val Arg
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cct gta acc  caa gga gat gtg tat  aga gct gaa act gaa  gaa att     4517
Pro Val Thr  Gln Gly Asp Val Tyr  Arg Ala Glu Thr Glu  Glu Ile
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cct aaa ata  ttc cag ata cta tat  gca aat gaa ggt gaa  tgt aga     4562
Pro Lys Ile  Phe Gln Ile Leu Tyr  Ala Asn Glu Gly Glu  Cys Arg
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aaa gat gta  gag atg gaa cca gta  caa caa gct gaa aaa  act aat     4607
Lys Asp Val  Glu Met Glu Pro Val  Gln Gln Ala Glu Lys  Thr Asn
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Phe Gln Asn  His Lys Gly His Glu  Phe Ile Pro Thr Leu  Tyr His
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Phe Pro Ala  Asn Cys Asp Ala Cys  Ala Lys Pro Leu Trp  His Val
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Phe Lys Pro  Pro Pro Ala Leu Glu  Cys Arg Arg Cys His  Val Lys
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Cys His Arg  Asp His Leu Asp Lys  Lys Glu Asp Leu Ile  Cys Pro
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Cys Lys Val  Ser Tyr Asp Val Thr  Ser Ala Arg Asp Met  Leu Leu
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Leu Ala Cys  Ser Gln Asp Glu Gln  Lys Lys Trp Val Thr  His Leu
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Ala Glu Asp Tyr Asp Val Val Lys Val Ile Gly Arg Gly Ala Phe Gly
    90                  95                  100

gaa gtg cag ttg gtt cgt cac aag gca tcg cag aag gtt tat gct atg       809
Glu Val Gln Leu Val Arg His Lys Ala Ser Gln Lys Val Tyr Ala Met
105                 110                 115                 120

aag ctt ctt agt aag ttt gaa atg ata aaa aga tca gat tct gcc ttt       857
Lys Leu Leu Ser Lys Phe Glu Met Ile Lys Arg Ser Asp Ser Ala Phe
                125                 130                 135

ttt tgg gaa gaa aga gat att atg gcc ttt gcc aat agc ccc tgg gtg       905
Phe Trp Glu Glu Arg Asp Ile Met Ala Phe Ala Asn Ser Pro Trp Val
            140                 145                 150

gtt cag ctt ttt tat gcc ttt caa gat gat agg tat ctg tac atg gta       953
Val Gln Leu Phe Tyr Ala Phe Gln Asp Asp Arg Tyr Leu Tyr Met Val
        155                 160                 165

atg gag tac atg cct ggt gga gac ctt gta aac ctt atg agt aat tat      1001
Met Glu Tyr Met Pro Gly Gly Asp Leu Val Asn Leu Met Ser Asn Tyr
    170                 175                 180

gat gtg cct gaa aaa tgg gcc aaa ttt tac act gct gaa gtt gtt ctt      1049
Asp Val Pro Glu Lys Trp Ala Lys Phe Tyr Thr Ala Glu Val Val Leu
185                 190                 195                 200

gct ctg gat gca ata cac tcc atg ggt tta ata cac aga gat gtg aag      1097
Ala Leu Asp Ala Ile His Ser Met Gly Leu Ile His Arg Asp Val Lys
                205                 210                 215

cct gac aac atg ctc ttg gat aaa cat gga cat cta aaa tta gca gat      1145
Pro Asp Asn Met Leu Leu Asp Lys His Gly His Leu Lys Leu Ala Asp
            220                 225                 230

ttt ggc acg tgt atg aag atg gat gaa aca ggc atg gta cat tgt gat      1193
Phe Gly Thr Cys Met Lys Met Asp Glu Thr Gly Met Val His Cys Asp
        235                 240                 245
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aca gca gtt gga aca ccg gat tat ata tca cct gag gtt ctg aaa tca      1241
Thr Ala Val Gly Thr Pro Asp Tyr Ile Ser Pro Glu Val Leu Lys Ser
    250                 255                 260

caa ggg ggt gat ggt ttc tat ggg cga gaa tgt gat tgg tgg tct gta      1289
Gln Gly Gly Asp Gly Phe Tyr Gly Arg Glu Cys Asp Trp Trp Ser Val
265                 270                 275                 280

ggt gtt ttc ctt tat gag atg cta gtg ggg gat act cca ttt tat gcg      1337
Gly Val Phe Leu Tyr Glu Met Leu Val Gly Asp Thr Pro Phe Tyr Ala
                285                 290                 295

gat tca ctt gta gga aca tat agc aaa att atg gat cat aag aat tca      1385
Asp Ser Leu Val Gly Thr Tyr Ser Lys Ile Met Asp His Lys Asn Ser
            300                 305                 310

ctg tgt ttc cct gaa gat gca gaa att tcc aaa cat gca aag aat ctc      1433
Leu Cys Phe Pro Glu Asp Ala Glu Ile Ser Lys His Ala Lys Asn Leu
        315                 320                 325

atc tgt gct ttc tta aca gat agg gag gta cga ctt ggg aga aat ggg      1481
Ile Cys Ala Phe Leu Thr Asp Arg Glu Val Arg Leu Gly Arg Asn Gly
    330                 335                 340

gtg gaa gaa atc aga cag cat cct ttc ttt aag aat gat cag tgg cat      1529
Val Glu Glu Ile Arg Gln His Pro Phe Phe Lys Asn Asp Gln Trp His
345                 350                 355                 360

tgg gat aac ata aga gaa acg gca gct cct gta gta cct gaa ctc agc      1577
Trp Asp Asn Ile Arg Glu Thr Ala Ala Pro Val Val Pro Glu Leu Ser
                365                 370                 375

agt gac ata gac agc agc aat ttc gat gac att gaa gat gac aaa gga      1625
Ser Asp Ile Asp Ser Ser Asn Phe Asp Asp Ile Glu Asp Asp Lys Gly
            380                 385                 390

gat gta gaa acc ttc cca att cct aaa gct ttt gtt gga aat cag ctg      1673
Asp Val Glu Thr Phe Pro Ile Pro Lys Ala Phe Val Gly Asn Gln Leu
        395                 400                 405

cct ttc atc gga ttt acc tac tat aga gaa aat tta tta tta agt gac      1721
Pro Phe Ile Gly Phe Thr Tyr Tyr Arg Glu Asn Leu Leu Leu Ser Asp
    410                 415                 420

tct cca tct tgt aga gaa act gat tcc ata caa tca agg aaa aat gaa      1769
Ser Pro Ser Cys Arg Glu Thr Asp Ser Ile Gln Ser Arg Lys Asn Glu
425                 430                 435                 440

gaa agt caa gag att cag aaa aaa ctg tat aca tta gaa gaa cat ctt      1817
Glu Ser Gln Glu Ile Gln Lys Lys Leu Tyr Thr Leu Glu Glu His Leu
                445                 450                 455

agc aat gag atg caa gcc aaa gag gaa ctg gaa cag aag tgc aaa tct      1865
Ser Asn Glu Met Gln Ala Lys Glu Glu Leu Glu Gln Lys Cys Lys Ser
            460                 465                 470

gtt aat act cgc cta gaa aaa aca gca aag gag cta gaa gag gag att      1913
Val Asn Thr Arg Leu Glu Lys Thr Ala Lys Glu Leu Glu Glu Glu Ile
        475                 480                 485

acc tta cgg aaa agt gtg gaa tca gca tta aga cag tta gaa aga gaa      1961
Thr Leu Arg Lys Ser Val Glu Ser Ala Leu Arg Gln Leu Glu Arg Glu
    490                 495                 500

aag gcg ctt ctt cag cac aaa aat gca gaa tat cag agg aaa gct gat      2009
Lys Ala Leu Leu Gln His Lys Asn Ala Glu Tyr Gln Arg Lys Ala Asp
505                 510                 515                 520

cat gaa gca gac aaa aaa cga aat ttg gaa aat gat gtt aac agc tta      2057
His Glu Ala Asp Lys Lys Arg Asn Leu Glu Asn Asp Val Asn Ser Leu
                525                 530                 535

aaa gat caa ctt gaa gat ttg aaa aaa aga aat caa aac tct caa ata      2105
Lys Asp Gln Leu Glu Asp Leu Lys Lys Arg Asn Gln Asn Ser Gln Ile
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tcc act gag aaa gtg aat caa ctc cag aga caa ctg gat gaa acc aat     2153
Ser Thr Glu Lys Val Asn Gln Leu Gln Arg Gln Leu Asp Glu Thr Asn
        555                 560                 565

gct tta ctg cga aca gag tct gat act gca gcc cgg tta agg aaa acc     2201
Ala Leu Leu Arg Thr Glu Ser Asp Thr Ala Ala Arg Leu Arg Lys Thr
    570                 575                 580

cag gca gaa agt tca aaa cag att cag cag ctg gaa tct aac aat aga     2249
Gln Ala Glu Ser Ser Lys Gln Ile Gln Gln Leu Glu Ser Asn Asn Arg
585                 590                 595                 600

gat cta caa gat aaa aac tgc ctg ctg gag act gcc aag tta aaa ctt     2297
Asp Leu Gln Asp Lys Asn Cys Leu Leu Glu Thr Ala Lys Leu Lys Leu
                605                 610                 615

gaa aag gaa ttt atc aat ctt cag tca gct cta gaa tct gaa agg agg     2345
Glu Lys Glu Phe Ile Asn Leu Gln Ser Ala Leu Glu Ser Glu Arg Arg
            620                 625                 630

gat cga acc cat gga tca gag ata att aat gat tta caa ggt aga ata     2393
Asp Arg Thr His Gly Ser Glu Ile Ile Asn Asp Leu Gln Gly Arg Ile
        635                 640                 645

tgt ggc cta gaa gaa gat tta aag aac ggc aaa atc tta cta gcg aaa     2441
Cys Gly Leu Glu Glu Asp Leu Lys Asn Gly Lys Ile Leu Leu Ala Lys
    650                 655                 660

gta gaa ctg gag aag aga caa ctt cag gag aga ttt act gat ttg gaa     2489
Val Glu Leu Glu Lys Arg Gln Leu Gln Glu Arg Phe Thr Asp Leu Glu
665                 670                 675                 680

aag gaa aaa agc aac atg gaa ata gat atg aca tac caa cta aaa gtt     2537
Lys Glu Lys Ser Asn Met Glu Ile Asp Met Thr Tyr Gln Leu Lys Val
                685                 690                 695

ata cag cag agc cta gaa caa gaa gaa gct gaa cat aag gcc aca aag     2585
Ile Gln Gln Ser Leu Glu Gln Glu Glu Ala Glu His Lys Ala Thr Lys
            700                 705                 710

gca cga cta gca gat aaa aat aag atc tat gag tcc atc gaa gaa gcc     2633
Ala Arg Leu Ala Asp Lys Asn Lys Ile Tyr Glu Ser Ile Glu Glu Ala
        715                 720                 725

aaa tca gaa gcc atg aaa gaa atg gag aag aag ctc ttg gag gaa aga     2681
Lys Ser Glu Ala Met Lys Glu Met Glu Lys Lys Leu Leu Glu Glu Arg
    730                 735                 740

act tta aaa cag aaa gtg gag aac cta ttg cta gaa gct gag aaa aga     2729
Thr Leu Lys Gln Lys Val Glu Asn Leu Leu Leu Glu Ala Glu Lys Arg
745                 750                 755                 760

tgt tct cta tta gac tgt gac ctc aaa cag tca cag cag aaa ata aat     2777
Cys Ser Leu Leu Asp Cys Asp Leu Lys Gln Ser Gln Gln Lys Ile Asn
                765                 770                 775

gag ctc ctt aaa cag aaa gat gtg cta aat gag gat gtt aga aac ctg     2825
Glu Leu Leu Lys Gln Lys Asp Val Leu Asn Glu Asp Val Arg Asn Leu
            780                 785                 790

aca tta aaa ata gag caa gaa act cag aag cgc tgc ctt aca caa aat     2873
Thr Leu Lys Ile Glu Gln Glu Thr Gln Lys Arg Cys Leu Thr Gln Asn
        795                 800                 805

gac ctg aag atg caa aca caa cag gtt aac aca cta aaa atg tca gaa     2921
Asp Leu Lys Met Gln Thr Gln Gln Val Asn Thr Leu Lys Met Ser Glu
    810                 815                 820

aag cag tta aag caa gaa aat aac cat ctc atg gaa atg aaa atg aac     2969
Lys Gln Leu Lys Gln Glu Asn Asn His Leu Met Glu Met Lys Met Asn
825                 830                 835                 840

ttg gaa aaa caa aat gct gaa ctt cga aaa gaa cgt cag gat gca gat     3017
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Leu Glu Lys Gln Asn Ala Glu Leu Arg Lys Glu Arg Gln Asp Ala Asp
                845                 850                 855

ggg caa atg aaa gag ctc cag gat cag ctc gaa gca gaa cag tat ttc    3065
Gly Gln Met Lys Glu Leu Gln Asp Gln Leu Glu Ala Glu Gln Tyr Phe
            860                 865                 870

tca acc ctt tat aaa aca caa gtt agg gag ctt aaa gaa gaa tgt gaa    3113
Ser Thr Leu Tyr Lys Thr Gln Val Arg Glu Leu Lys Glu Glu Cys Glu
        875                 880                 885

gaa aag acc aaa ctt ggt aaa gaa ttg cag cag aag aaa cag gaa tta    3161
Glu Lys Thr Lys Leu Gly Lys Glu Leu Gln Gln Lys Lys Gln Glu Leu
    890                 895                 900

cag gat gaa cgg gac tct ttg gct gcc caa ctg gag atc acc ttg acc    3209
Gln Asp Glu Arg Asp Ser Leu Ala Ala Gln Leu Glu Ile Thr Leu Thr
905                 910                 915                 920

aaa gca gat tct gag caa ctg gct cgt tca att gct gaa gaa caa tat    3257
Lys Ala Asp Ser Glu Gln Leu Ala Arg Ser Ile Ala Glu Glu Gln Tyr
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tct gat ttg gaa aaa gag aag atc atg aaa gag ctg gag atc aaa gag    3305
Ser Asp Leu Glu Lys Glu Lys Ile Met Lys Glu Leu Glu Ile Lys Glu
            940                 945                 950

atg atg gct aga cac aaa cag gaa ctt acg gaa aaa gat gct aca att    3353
Met Met Ala Arg His Lys Gln Glu Leu Thr Glu Lys Asp Ala Thr Ile
        955                 960                 965

gct tct ctt gag gaa act aat agg aca cta act agt gat gtt gcc aat    3401
Ala Ser Leu Glu Glu Thr Asn Arg Thr Leu Thr Ser Asp Val Ala Asn
    970                 975                 980

ctt gca aat gag aaa gaa gaa tta aat aac aaa ttg aaa gat gtt caa    3449
Leu Ala Asn Glu Lys Glu Glu Leu Asn Asn Lys Leu Lys Asp Val Gln
985                 990                 995                 1000

gag caa ctg tca aga  ttg aaa gat gaa gaa  ata agc gca gca gct      3494
Glu Gln Leu Ser Arg  Leu Lys Asp Glu Glu  Ile Ser Ala Ala Ala
                1005                1010                1015

att aaa gca cag ttt  gag aag cag cta tta  aca gaa aga aca ctc      3539
Ile Lys Ala Gln Phe  Glu Lys Gln Leu Leu  Thr Glu Arg Thr Leu
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aaa act caa gct gtg  aat aag ttg gct gag  atc atg aat cga aaa      3584
Lys Thr Gln Ala Val  Asn Lys Leu Ala Glu  Ile Met Asn Arg Lys
                1035                1040                1045

gaa cct gtc aag cgt  ggt aat gac aca gat  gtg cgg aga aaa gag      3629
Glu Pro Val Lys Arg  Gly Asn Asp Thr Asp  Val Arg Arg Lys Glu
                1050                1055                1060

aag gag aat aga aag  cta cat atg gag ctt  aaa tct gaa cgt gag      3674
Lys Glu Asn Arg Lys  Leu His Met Glu Leu  Lys Ser Glu Arg Glu
                1065                1070                1075

aaa ttg acc cag cag  atg atc aag tat cag  aaa gaa ctg aat gaa      3719
Lys Leu Thr Gln Gln  Met Ile Lys Tyr Gln  Lys Glu Leu Asn Glu
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atg cag gca caa ata  gct gaa gag agc cag  att cga att gaa ctg      3764
Met Gln Ala Gln Ile  Ala Glu Glu Ser Gln  Ile Arg Ile Glu Leu
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cag atg aca ttg gac  agt aaa gac agt gac  att gag cag ctg cgg      3809
Gln Met Thr Leu Asp  Ser Lys Asp Ser Asp  Ile Glu Gln Leu Arg
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tca caa ctc caa gcc  ttg cat att ggt ctg  gat agt tcc agt ata      3854
Ser Gln Leu Gln Ala  Leu His Ile Gly Leu  Asp Ser Ser Ser Ile
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ggc agt gga cca ggg  gat gct gag gca gat  gat ggg ttt cca gaa      3899
Gly Ser Gly Pro Gly  Asp Ala Glu Ala Asp  Asp Gly Phe Pro Glu
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tca aga tta gaa gga  tgg ctt tca ttg cct  gta cga aac aac act      3944
Ser Arg Leu Glu Gly  Trp Leu Ser Leu Pro  Val Arg Asn Asn Thr
                1155                1160                1165

aag aaa ttt gga tgg  gtt aaa aag tat gtg  att gta agc agt aag      3989
Lys Lys Phe Gly Trp  Val Lys Lys Tyr Val  Ile Val Ser Ser Lys
                1170                1175                1180

aag att ctt ttc tat  gac agt gaa caa gat  aaa gaa caa tcc aat      4034
Lys Ile Leu Phe Tyr  Asp Ser Glu Gln Asp  Lys Glu Gln Ser Asn
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cct tac atg gtt tta  gat ata gac aag tta  ttt cat gtc cga cca      4079
Pro Tyr Met Val Leu  Asp Ile Asp Lys Leu  Phe His Val Arg Pro
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gtt aca cag aca gat  gtg tat aga gca gat  gct aaa gaa att cca      4124
Val Thr Gln Thr Asp  Val Tyr Arg Ala Asp  Ala Lys Glu Ile Pro
                1215                1220                1225

agg ata ttc cag att  ctg tat gcc aat gaa  gga gaa agt aag aag      4169
Arg Ile Phe Gln Ile  Leu Tyr Ala Asn Glu  Gly Glu Ser Lys Lys
                1230                1235                1240

gaa caa gaa ttt cca  gtg gag cca gtt gga  gaa aaa tct aat tat      4214
Glu Gln Glu Phe Pro  Val Glu Pro Val Gly  Glu Lys Ser Asn Tyr
                1245                1250                1255

att tgc cac aag gga  cat gag ttt att cct  act ctt tat cat ttc      4259
Ile Cys His Lys Gly  His Glu Phe Ile Pro  Thr Leu Tyr His Phe
                1260                1265                1270

cca acc aac tgt gag  gct tgt atg aag ccc  ctg tgg cac atg ttt      4304
Pro Thr Asn Cys Glu  Ala Cys Met Lys Pro  Leu Trp His Met Phe
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aag cct cct cct gct  ttg gag tgc cgc cgt  tgc cat att aag tgt      4349
Lys Pro Pro Pro Ala  Leu Glu Cys Arg Arg  Cys His Ile Lys Cys
                1290                1295                1300

cat aaa gat cat atg  gac aaa aag gag gag  att ata gca cct tgc      4394
His Lys Asp His Met  Asp Lys Lys Glu Glu  Ile Ile Ala Pro Cys
                1305                1310                1315

aaa gta tat tat gat  att tca acg gca aag  aat ctg tta tta cta      4439
Lys Val Tyr Tyr Asp  Ile Ser Thr Ala Lys  Asn Leu Leu Leu Leu
                1320                1325                1330

gca aat tct aca gaa  gag cag cag aag tgg  gtt agt cgg ttg gtg      4484
Ala Asn Ser Thr Glu  Glu Gln Gln Lys Trp  Val Ser Arg Leu Val
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aaa aag ata cct aaa  aag ccc cca gct cca  gac cct ttt gcc cga      4529
Lys Lys Ile Pro Lys  Lys Pro Pro Ala Pro  Asp Pro Phe Ala Arg
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Ser Ser Pro Arg Thr  Ser Met Lys Ile Gln  Gln Asn Gln Ser Ile
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Gly Leu Asn Ser Leu Val Leu Asp Leu Asp Phe Pro Ala Leu Arg Lys
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Asn Lys Asn Ile Asp Asn Phe Leu Asn Arg Tyr Glu Lys Ile Val Lys
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Lys Ile Arg Gly Leu Gln Met Lys Ala Glu Asp Tyr Asp Val Val Lys
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Val Ile Gly Arg Gly Ala Phe Gly Glu Val Gln Leu Val Arg His Lys
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Ala Ser Gln Lys Val Tyr Ala Met Lys Leu Leu Ser Lys Phe Glu Met
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Phe Tyr Thr Ala Glu Val Val Leu Ala Leu Asp Ala Ile His Ser Met
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Gly Leu Ile His Arg Asp Val Lys Pro Asp Asn Met Leu Leu Asp Lys
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His Gly His Leu Lys Leu Ala Asp Phe Gly Thr Cys Met Lys Met Asp
225 230 235 240

Glu Thr Gly Met Val His Cys Asp Thr Ala Val Gly Thr Pro Asp Tyr
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Ile Ser Pro Glu Val Leu Lys Ser Gln Gly Gly Asp Gly Phe Tyr Gly
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Val Gly Asp Thr Pro Phe Tyr Ala Asp Ser Leu Val Gly Thr Tyr Ser
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Lys Ile Met Asp His Lys Asn Ser Leu Cys Phe Pro Glu Asp Ala Glu
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Ile Ser Lys His Ala Lys Asn Leu Ile Cys Ala Phe Leu Thr Asp Arg
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835 840 845

Arg Lys Glu Arg Gln Asp Ala Asp Gly Gln Met Lys Glu Leu Gln Asp
850 855 860

Gln Leu Glu Ala Glu Gln Tyr Phe Ser Thr Leu Tyr Lys Thr Gln Val
865 870 875 880

Arg Glu Leu Lys Glu Glu Cys Glu Glu Lys Thr Lys Leu Gly Lys Glu
885 890 895

Leu Gln Gln Lys Lys Gln Glu Leu Gln Asp Glu Arg Asp Ser Leu Ala
900 905 910

Ala Gln Leu Glu Ile Thr Leu Thr Lys Ala Asp Ser Glu Gln Leu Ala
915 920 925

Arg Ser Ile Ala Glu Glu Gln Tyr Ser Asp Leu Glu Lys Glu Lys Ile
930 935 940

Met Lys Glu Leu Glu Ile Lys Glu Met Met Ala Arg His Lys Gln Glu
945 950 955 960

Leu Thr Glu Lys Asp Ala Thr Ile Ala Ser Leu Glu Glu Thr Asn Arg
965 970 975

Thr Leu Thr Ser Asp Val Ala Asn Leu Ala Asn Glu Lys Glu Glu Leu
980 985 990

Asn Asn Lys Leu Lys Asp Val Gln Glu Gln Leu Ser Arg Leu Lys Asp
995 1000 1005

Glu Glu Ile Ser Ala Ala Ala Ile Lys Ala Gln Phe Glu Lys Gln
1010 1015 1020

Leu Leu Thr Glu Arg Thr Leu Lys Thr Gln Ala Val Asn Lys Leu
1025 1030 1035

Ala Glu Ile Met Asn Arg Lys Glu Pro Val Lys Arg Gly Asn Asp
1040 1045 1050

Thr Asp Val Arg Arg Lys Glu Lys Glu Asn Arg Lys Leu His Met
1055 1060 1065

Glu Leu Lys Ser Glu Arg Glu Lys Leu Thr Gln Gln Met Ile Lys
1070 1075 1080

Tyr Gln Lys Glu Leu Asn Glu Met Gln Ala Gln Ile Ala Glu Glu
1085 1090 1095

Ser Gln Ile Arg Ile Glu Leu Gln Met Thr Leu Asp Ser Lys Asp
1100 1105 1110

Ser Asp Ile Glu Gln Leu Arg Ser Gln Leu Gln Ala Leu His Ile
1115 1120 1125

Gly Leu Asp Ser Ser Ser Ile Gly Ser Gly Pro Gly Asp Ala Glu
1130 1135 1140

Ala Asp Asp Gly Phe Pro Glu Ser Arg Leu Glu Gly Trp Leu Ser
1145 1150 1155

Leu Pro Val Arg Asn Asn Thr Lys Lys Phe Gly Trp Val Lys Lys
1160 1165 1170

Tyr Val Ile Val Ser Ser Lys Lys Ile Leu Phe Tyr Asp Ser Glu
1175 1180 1185

Gln Asp Lys Glu Gln Ser Asn Pro Tyr Met Val Leu Asp Ile Asp
1190 1195 1200

Lys Leu Phe His Val Arg Pro Val Thr Gln Thr Asp Val Tyr Arg
1205 1210 1215

Ala Asp Ala Lys Glu Ile Pro Arg Ile Phe Gln Ile Leu Tyr Ala
1220 1225 1230

Asn Glu Gly Glu Ser Lys Lys Glu Gln Glu Phe Pro Val Glu Pro
1235 1240 1245

Val Gly Glu Lys Ser Asn Tyr Ile Cys His Lys Gly His Glu Phe
1250 1255 1260

Ile Pro Thr Leu Tyr His Phe Pro Thr Asn Cys Glu Ala Cys Met
1265 1270 1275

Lys Pro Leu Trp His Met Phe Lys Pro Pro Pro Ala Leu Glu Cys
1280 1285 1290

Arg Arg Cys His Ile Lys Cys His Lys Asp His Met Asp Lys Lys
1295 1300 1305

Glu Glu Ile Ile Ala Pro Cys Lys Val Tyr Tyr Asp Ile Ser Thr
1310 1315 1320

Ala Lys Asn Leu Leu Leu Leu Ala Asn Ser Thr Glu Glu Gln Gln
1325 1330 1335

Lys Trp Val Ser Arg Leu Val Lys Lys Ile Pro Lys Lys Pro Pro
1340 1345 1350

Ala Pro Asp Pro Phe Ala Arg Ser Ser Pro Arg Thr Ser Met Lys
1355 1360 1365

Ile Gln Gln Asn Gln Ser Ile Arg Arg Pro Ser Arg Gln Leu Ala
1370 1375 1380

Pro Asn Lys Pro Ser
1385